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Allergic Reactions to ACTH

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The use of adrenocorticotropic hormone (ACTH) has become established as an effective and generally safe method of therapy. Its value in allergic disorders is outstanding and we would find it difficult to practice without it. As with many effective drugs, however, there is a tendency toward overuse, and we are therefore reporting eight cases of allergic reactions to ACTH in an effort to re-emphasize the risks involved with its use.

The objectionable effects of ACTH therapy may be divided into three general categories. First, there are the usual side effects found especially in patients receiving large dosages for prolonged periods of time. Cushing's syndrome is a final phase of this problem but milder effects, *e.g.*, weight gain and moon facies may occur even with small amounts. Next there are certain pre-existing diseases which may be aggravated by ACTH and other steroids, *e.g.*, peptic ulcers, tuberculosis and diabetes. Finally, there are those conditions which are presumably on an antigen-antibody basis, characterized by urticaria, asthma, shock and sometimes death, unrelated to dosage or pre-existing diseases, and which may occur in patients who often demonstrate positive skin tests to the offending materials. We believe that the following cases fall into this last group.

Case Reports

Case 1: AG—This 59 year-old white man had a 25-year history of asthma and rhinitis, as well as a mild diabetes mellitus. He was first given ACTH gel (Armour) twice a day for about a week in December, 1955, and subsequently received seven more such injections at varying intervals with no apparent ill effects. On April 24, 1957, he was again given 40 units of ACTH-gel (Armour); 30 minutes later he became dyspneic, cyanotic, and developed severe wheezing and coughing. His blood pressure was unobtainable, but following emergency treatment with oxygen, epinephrine, intravenous aminophyllin and coramine he recovered rapidly. Electrocardiograms were unchanged. A month later scratch tests were read as follows:

0	Lamb, beef, pork
0	Armour ACTH gel 80 units
1 plus	Acthar HP 10 units (lyophylized)
2 plus	Acthar HP 25 units (lyophylized)
4 plus	Acthar HP 40 units (lyophylized)
2 plus	Wilson ACTH gel 40 units
1 plus	Corticotrophin zinc 40 units

Case 2: Mrs. P. D.—This 45 year-old white housewife had a 25-year history of intermittent severe asthma and rhinitis. Because of the severity of symptoms she

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received ACTH both as a gel and an intravenous drip on several occasions between 1954 and 1957. In May, 1957, she was given 40 units of ACTH (Armour) to "pep up her adrenals" as she had been on prednisone for a year. She quickly developed generalized urticaria, angioneurotic edema of her left eye and ear lobes, and lost her voice. She recovered rapidly and uneventfully. Scratch tests gave the following results:

0	10 units of ACTH gel (Armour)
2 plus	25 units ACTH gel (Armour)
4 plus	40 units ACTH gel (Armour) (lyophylized)
2 plus	80 units ACTH gel (Armour)
1 plus	Corticotrophin Zinc (Organon)
0	Control
0	Beef
1 plus	Pork
2 plus	Bovine ACTH (saline)—Armour
2 plus	Porcine ACTH (saline)—Armour
0	Gelatin

Case 3: J.N.—This 67 year-old maintenance worker was first given ACTH in 1954 in an intravenous drip with aminophyllin because of intractable asthma. Six months later he was re-hospitalized and treated identically. During the second liter containing 20 units of ACTH and 20 cc. of aminophyllin he suddenly became dyspneic, confused, and developed convulsive movements of his extremities. His breathing was rapid and gasping, and his eyeballs rolled back. The attack lasted about two hours, after which he complained of pain in his left shoulder. X-ray films revealed an impacted fracture of the anatomical neck of the humerus, from which he recovered uneventfully. He has subsequently received aminophyllin on numerous occasions without difficulty.

We were never able to skin-test the patient or identify the brand of soluble ACTH used in this patient.

Case 4: M.G.—This 25 year-old woman was first seen by us in January, 1954, because of urticaria present intermittently for one month despite treatment with antihistamines, cortisone, ACTH and diets. Two months previously she had been given a series of penicillin injections as well as penicillin inhalations for a sinus infection. She had a "mild attack of rheumatic fever" as a child. On examination there were many carious teeth, some suprapubic tenderness and an extremely tender urethra, but no cardiac abnormality was found. Treatment with chlorpheniramine maleate (Chlortrimeton), diphenhydramine hydrochloride (Benadryl) and elimination diets failed to produce improvements, so a series of five ACTH gel injections were given. Three months later she was hospitalized and given 20 units of ACTH gel (Armour). Thirty minutes later she had an epileptiform seizure following which she was weak, confused and vomited once. Her reflexes were brisk in the lower extremities, with a positive Babinski sign bilaterally and questionable ankle clonus on the left. All medication was stopped and her symptoms were treated with sodium amytal. Electroencephalograms revealed "mildly abnormal five second slowing bifrontally and bitemporally in the waking state." This was considered to be negative for epilepsy. She refused to have skin tests for ACTH. In the past six years she has had no further neurologic episodes.

This patient stated that there was no previous history of epilepsy either in herself or in her family.

Case 5: J.F.—This 55 year-old salesman had a 17-year history of chronic asthma when he was first given ACTH in 1952. Subsequently he received ACTH both as the gel and in an intravenous drip on several occasions without incident until 1957 when he was restarted on a drip containing 20 units of Wilson's corticotropin in 1000 cc. 5 per cent glucose in water. Almost immediately he developed increasing dyspnea, generalized urticaria, and angioneurotic edema of the face and eyelids. The drip was stopped and epinephrine and Benadryl administered. The urticaria recurred intermittently for two to three months. We were never able to skin test this patient.

Case 6: M.Z.—This 44 year-old woman gave a six-year history of asthma requiring treatment with ACTH gel and drip on several occasions. She had numerous positive intradermal skin tests. In January, 1960, she was again treated with an intravenous drip of 5 per cent glucose in water containing 20 units of ACTH (brand unknown) 20 cc. (0.5 gram) of aminophyllin and 1 cc. of 1:1000 epinephrine. Two hours later she developed generalized urticaria, followed by hoarseness and abdominal pain. Hydrocortisone was substituted for the ACTH in the drip, and Chlortrimeton administered. Symptoms subsided in four or five hours.

Scratch tests revealed the following results:

3 plus	Organon purified corticotrophin gel
3 plus	Armour Acthar HP 80 units
2 plus	Armour Porcine ACTH
0	Armour Bovine ACTH
4 plus	Armour Acthar (lyophylized) 25 units
3 plus	Armour Acthar 40 units
0	Beef
0	Pork

Case 7: M.K.—This 56 year-old woman had had asthma for 23 years, with symptoms almost constantly for the past two years. She had numerous positive intradermal skin tests. She was treated with intravenous drip ACTH in June, 1959, and had received ACTH gel three times without difficulty, when in April, 1960, she was again given an intravenous drip of ACTH (National) with aminophyllin and epinephrine because of intractable asthma. One and one half hours later she developed generalized urticaria which was treated successfully with Benadryl; hydrocortisone was substituted for ACTH in the intravenous drip. Scratch tests for ACTH were completely negative.

Case 8: A.C.—This 68 year-old man had asthma for 12 years. Skin tests were almost negative and "P pulmonale" was present on his electrocardiogram. Between 1948 and 1959 he received ACTH on several occasions, both as the gel and in an intravenous drip. In November, 1959, he was restarted on the drip because of severe asthma. About two hours later he suddenly became maniacal with shouting, jerking, disorientation, tremors, confusion and urinary incontinence. The entire episode lasted only five minutes, being relieved by 75 mg. of meperidine hydrochloride (Demerol) and discontinuance of the intravenous drip. Subsequently neulogic examination revealed only minimal non-specific changes, a lumbar puncture (bloody tap) failed to show increased pressure, and an electroencephalogram was read as "much disorganization of the basic frequencies, but not epileptic."

Skin tests to ACTH were completely negative, and he has had no further neurologic difficulties.

Discussion

Allergic reactions apparently due to ACTH may be caused by sensitivity to any of the following:

1. ACTH itself.
2. The vehicle or preservative injected with the ACTH, *e.g.*, gelatin.
3. The animal source from which the ACTH was derived, *e.g.*, pork or beef.
4. A contaminant introduced by the manufacturer, or
5. A contaminant in the syringe, *e.g.*, penicillin.

Our reactions occurred to Armour, Wilson and National Drug Company material so contamination by any one manufacturer can be ruled out. Those patients who exhibited positive skin tests to the materials, invariably reacted to various types of ACTH but not to the gelatin, pork or beef. Five of the eight patients had their allergic reactions to the ACTH intravenous drip so it is unlikely that any contamination of tubing or syringes could have taken place in them. Also, once a syringe has been used for penicillin in our office, it is never used for anything else.

About 1957 we abandoned the use of intermittent injections of ACTH to "pep up" the adrenals of patients on long-term steroid therapy, as it was shown to be probably ineffective for this purpose. We feel, however, that the intraveonus drip of ACTH in status asthmaticus is so effective that it is more than worth the risks involved. This is why our later patients reacted to the drip—we rarely used the gel.

Allergic reactions to ACTH have been reported by numerous investigators since 1950,[1-17] symptoms ranging from urticaria to death. Some observers[4,5] feel that there is a definite relationship between ACTH therapy and convulsions, and suggest that ACTH may induce convulsions in predisposed (occult) epileptics, just as it might precipitate diabetes in susceptible individuals. Dorfman[6] reported status epilepticus with subsequent brain damage in three of 40 rheumatic children treated with ACTH, in the absence of associated hypertension or electrolyte inbalance. Hoefer and Glaser[7] discuss electroencephalographic abnormalities under such circumstances, while Wayne[8] describes four of 43 patients who had convulsions from ACTH. Bonham[9] had a patient die from convulsions following treatment with ACTH and cortisone, no specific abnormality being found at autopsy.

If these convulsions were on an allergic basis, the patients might have positive skin tests to ACTH, as do many patients who have had hives, asthma or shock following the drug. On the other hand, if the reactions were due to a predisposition to epilepsy,

no such skin reactions would be expected. It is unfortunate that we were able to skin test only one of our three patients with cerebral manifestations; his tests were negative.

Anaphylactic shock was reported from an ACTH drip by Anderson[10] and by Wilson,[11] but Wilson later gave one of his patients ACTH gel uneventfully. Anaphylaxis occurred in seven patients described by Brown and Hollander,[2] and Fisalo[12] had a patient expire within 15 minutes of an injection. Others have also reported such severe reactions.[13-15]

Skin testing with ACTH has been performed by several investigators with varying results. Perkoff *et al.*[14] showed that in individuals sensitive to corticotrophin, positive reactions may be restricted to preparations from a particular species or may extend to ACTH derived from many different animals (sheep, pig, horse, and whale pituitary). Their patients' serum was found to retain passively transferrable, reagin-like antibodies to several corticotrophin preparations for at least 16 months after the anaphylactic reaction.

The cases reported by Swift[16] and Feinberg *et al.*[3] showed skin sensitivity to several species of ACTH. On the other hand, several of the patients reported by Brown and Hollander[2] were later able to tolerate a beef gland preparation instead of the usual commercial pork product.

Arnoldsson[13] states, "In ten cases with manifest reactions to ACTH, intradermal tests have been made at regular intervals. It has been demonstrated that the skin reactions weaken in a number of cases after a period of six to 12 months. In these latter cases, we have again been able to administer ACTH without complications." He believes that his cases were due to a specific hypersensitivity to the hormone. In our cases we reached a similar conclusion, but would avoid using ACTH under any circumstances in a patient who has reacted adversely to it.

SUMMARY

1. Sensitization to ACTH is becoming more frequent; symptoms may include urticaria, angio-edema, convulsions, shock and death.

2. Eight reactions are reported including three with cerebral manifestations and one with shock.

3. Convulsions may be due to either an allergy or a predisposition to epilepsy. We were unable to determine which of the two was present in our three patients.

4. Our reactions were probably due to ACTH itself, rather than to any contaminating antigen.

5. ACTH remains a valuable drug, but should be used only when indicated. Once a patient has reacted to it, he should not receive it again.

RESUMEN

1. La sensibilización al ACTH se esta haciendo más frecuente; los sintomas pueden incluir urticaria, angio-edema, convulsiones, schock y muerte.

2. Se relatan ocho reacciones, comprendiendo tres con manifestaciones cerebrales y una con schock.

3. Las convulsiones pueden deberse ya sea a la alergia o al predisposición a la epilepsia. No pudimos determinar de cual de esas causas se debía en nuestros tres enfermos.

4. Las reacciones que observamos se debieron probablemente al ACTH mismo y no a ningun otro antígeno contaminante.

5. El ACTH sigue siendo una droga valiosa pero debe usarse cuando ésta indicada. Una vez que en enfermo ha reaccionado a ella ya no debe volver a usarse.

ZUSAMMENFASSUNG

1. Sensibilisierung gegenüber ACTH wird häufiger; ihre Symptome können sich erstrecken auf Urtikarie, Gefäßödeme, Krämpfe, Schock und Tod.

2. Bericht über 8 Reaktionen einschliesslich 3 mit cerebralen Manifestationen und einem mit Schock.

3. Krämpfe können entweder die Folge einer Allergie sein oder einer Prädisposition zu Epilepsie. Es war uns nicht möglich, zu bestimmen, welcher dieser beiden Momente bei unseren 3 Kranken vorlag.

4. Unsere Reaktionen waren wahrscheinlich eher dem ACTH selbst zu zuschreiben als irgend einem verunreinigenden Antigen.

5. ACTH bleibt ein wertvolles Arzneimittel, sollte aber nur dann angewandt werden, wenn es indiziert ist. Hat einmal ein Kranker darauf ungünstig reagiert, sollte man es ihm nie wieder geben.

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REGULATORY MECHANISMS OF PULMONARY PRESSURE IN CONGESTIVE HEART DISEASES

The most important factors which participate in the regulation of the pulmonary pressure in congenital heart diseases with left to right shunts (patent ductus arteriosus, atrial septal defect and ventricular septal defect) were studied.

The main factors responsible for pulmonary hypertension in these types of heart disease are essentially of a functional nature.

A probable reduction in the partial pressure of oxygen in the blood of the pulmonary veins causes a reflex vasoconstriction of the precapillary arterioles of the lung. The reduction of a PaO_2 is due both to a low partial oxygen pressure in the air at altitudes above 1.500 meters and to impaired blood oxygenation relative to a pulmonary hypervolemia. Although the reflex vasoconstriction is not the main factor, it is an important one in the regulation of pulmonary pressure. Other factors include the increased energy of contraction of the right ventricle, the transmission of the systemic pressure to the pulmonary circulation, and the "pseudomitral syndrome." When the last two mechanisms are lacking, as in the case of atrial septal defect, pulmonary hypertension if uncommon.

All of these factors are susceptible to being reduced or eliminated with the surgical treatment of the malformation.

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Comments on Some Controversial Questions of Bronchial Classification and Nomenclature

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Certain problems of the bronchial anatomy still call for a solution despite the fact that these questions have been discussed by numerous outstanding researchers on grounds of embriology, comparative anatomy, investigation of human bronchial trees, mechanical factors andaerodynamic laws of respiration, so thoroughly that it seems almost impossible to find any other important factor involved in these questions. However, evaluation from a clinician's point of view or other factors may serve our purpose to bring some problems closer to solution. This is what I intend to present in this paper.

The following details of the bronchial anatomy will be discussed:

1. The main, stem and lower lobe bronchi.
2. The lateral or axillary region of the upper lobes.
3. The superior or apical segment of the lower lobes.
4. Subsuperior segment of the lower lobes.
5. Medial basal segments.
6. Homology of the two lungs.

I venture to enter on these complex problems after analyzing about 2,000 bronchograms and more than 250 right and 250 left human bronchial trees. Seventy of these were prepared by myself or with Labas; the others were the specimens of the Departments of Medical Jurisprudence and Anatomy of the University of Budapest School of Medicine. I also prepared about 30 animal bronchial trees (dog, cat, rabbit, rat). These studies are being continued in the Research Division of the Lankenau Hospital, Philadelphia.

1. Main, Stem and Lower Lobe Bronchi

Detailed investigation of the bronchial tree started with the classic work of Aeby, the Swiss anatomist, in 1880. In his theory, a "stem bronchus" gives off numerous side-branches *monopodially,* and this system is repeated on the side-branches again and again. Hence, the bronchial branchings are similar to that which one may observe in a pine tree.

Nine years later, in 1889, Ewart, English pathologist, criticized Aeby's system. Ewart felt that "man is the only mammal in which the existence of a 'bronchial stem' is difficult to recognize at a glance" and that all trace of it is lost below the orifice of the posterior basal bronchus. He believed that the basic pattern of the human bronchial branchings is *dichotomy,* which is more suitable to fill the short, broad, grossly barrel-shaped thorax of a man, resembling, in shape and branchings, an oak tree (Fig. 1).

His, in 1887, verified some of Aeby's interpretations with embryologic studies. He found that at four weeks of development of an embryo, the first buds appear on both stem bronchi as monopodial offshoots and then

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the lower lobe bronchus, as a "stem," repeats this process until it reaches the posteromedial inferior angle of the lungs. However, His differed from Aeby in interpretation of the further branchings of the monopodial offshoots. He found that these buds divide *dichotomously* and, in their subdivisions, they repeat this mode of branchings again and again.

Later investigators (Heiss, Wells and Boyden) found something to be corrected also in His' interpretation. They stated that the "stem" bronchus discontinues its axial growing at the beginning of the lower lobe bronchus. Boyden writes: "Growth of the lower lobe bronchus is not to be construed as an extension of the so-called stem bronchus but as a differentiation of a lobar bronchus."

This statement is confirmed by our knowledge of the structure of the bronchial wall. The lumina of the *trachea* and the *primary cartilaginous bronchi* (bronchi between the trachea and the origins of the lower lobe bronchus) are kept open by "C"—cartilages; the posterior wall, corresponding to the open portion of "C," is membranous.* In the *secondary cartilaginous bronchi,* which start with the five lobar bronchi, small plaques and lamellae of cartilage are imbedded in the soft tissues of the wall.

After the different applications of the term "stem" bronchus, the problem is whether this term can be properly applied to the trunk between the right upper and middle lobe bronchi as it is in common usage nowadays, or, because of its double connotation, drop and substitute it with a better term, or mode.

Boyden suggested to name the stem between the tracheal carina and middle lobe bronchus "primary bronchus." The Thoracic Surgical Society of Great Britain expanded the meaning of the term "main" bron-

*The exact distal limit of the membranous posterior wall is still dubious. I have seen it extend as far as the superior wall of bronchus 6. I do not have an adequate number of cases and find no data in the literature concerning this question. However, I believe that these bronchi are identical with that defined "stem" bronchus in embryology.

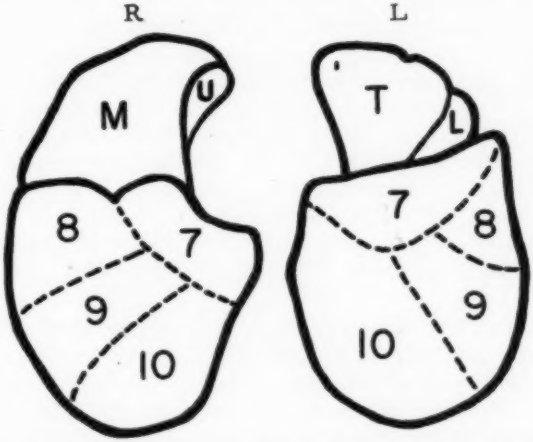

FIGURE 1: Diaphragmatic view of human lungs shown on sketch. R—right, L—left, U—upper lobe, M—middle lobe, T—truncated lobe, L—lingula; segments of the lower lobes are numbered. Note size and shape of the lower lobes and segments 7.

chus to this stem and subdivided it into upper and lower parts. Huber agrees with this classification and believes that "the bronchus from the bifurcation of the trachea to the division into middle and lower lobe bronchi can well be called either 'right main bronchus' or 'right lung bronchus.' The latter name is more in keeping with the rest of the terminology. The parts of this bronchus can then be designated as 'right main bronchus' or 'right lung bronchus' proximal to or distal to the upper lobe bronchus."

Boyden's term, "the primary bronchus," is borrowed from another type of classification which is useful in considering the bronchi according to their importance in branchings as primary, secondary, tertiary, etc., but seldom used in clinical work.

In the imagination of a clinician, a "main" bronchus supplies the *main* unit of the respiratory organ, the "lung." It seems logical to every clinician that if a right or left "main" bronchus is obstructed, in either case, a total lung is involved, but if the term "main" bronchus is adopted to the stem between the tracheal and middle lobe carina, entire involvement of a lung appears only in case of an obstruction of the *upper part* of the main bronchus. This also complicates clinical work, but I think that anatomically, it is also proper to adapt the most significant term to the most significant bronchus which supplies not only a portion, but the wholeness of a lung.

Nowadays, the generally accepted terms are "main" bronchus for the upper part and "stem" bronchus for the lower part of the bronchial stem of the right lung. These short terms were used with satisfaction in clinical work for decades. I do not think the term "stem" should be dropped because of its connotations. With such application of this term, a "bronchial stem" can be accepted in the right lung. The term "main" may mean the anatomically and clinically more important, the chief, the "main" part of the stem, and "stem" the remaining part of the stem. "Main" and "stem" may be accepted as simplification for clinical and anatomic purposes of the more expressive, but longer designations.

However, I believe that Huber's porposal is the most logical in naming the main trunk of both lungs "lung bronchus," and adjusting this term to the others, the "lobar and segmental bronchi." "Lung, lobe and segment bronchi" sound logical because each of them supplies the pulmonary unit given in the name. However, if the term "main bronchus" would be substituted with the term "lung bronchus," we still have a problem naming the stem between the right upper and middle lower bronchus, Probably Ewart's old term, "bronchus intermedius" in its Anglicized form "intermediate bronchus" fits this nomenclature, because this stem is really intermediate between the "lung" bronchus and the three "lobe" bronchi.

In case of the lower lobe bronchus, both question and answer are fairly similar to that discussed in the foregoing paragraphs. The question is: Which part of the lower lobe stem should be named "lower lobe bronchus," the short trunk above the bronchus 6 or the whole lower lobar trunk? Boyden believes that it is the short trunk; Huber thinks that it is the whole trunk and the parts of the lower lobe bronchus can be designated as "lower lobe bronchus between the superior (apical) seg-

mental bronchus and anterior segmental bronchus;" or, for example, "lower lobe bronchus just proximal or just distal to the medial basal bronchus."

I feel that the answer is already given in the question. If we talk about upper and lower parts of a trunk or stem, there is a trunk or stem which may divide in its embryologic period dichotomously (Heiss, Wells and Boyden), but the end result in adults is a *monopodial* branching. There is no problem as to which portion of the bronchial tree should be named "upper or middle lobe bronchus," because these lobar bronchi shoot off their segmental branches at once, at the same location, but the lower lobe bronchi give off their segmental branchings one after another, alternating their location on the different aspects of the stem bronchus. The branchings in the upper and middle lobes are dichotomous with apparent or spurious trifurcation in the right upper lobe (Ewart), but the branchings in the lower lobes are definitely *monopodial*.

A long stem undoubtedly exists in both lungs between the tracheal bifurcation and last basal segmental division and it ramifies monopodially. Every bronchologist, especially when using a bronchoscope with proximal illumination, recognizes this long stem and its monopodial side-branchings.

If we compare the ventral view of the right "main" and "stem" bronchus with the lateral view of the lower lobe branchings, the close similarity is indubitable. Therefore, the correct way is to harmonize this problem with that of the right "stem" bronchus.

In case of the lower lobe bronchus, the chief or main stem is the short trunk between the middle lobe bronchus and superior segmental bronchus of the lower lobe. This trunk supplies the whole lower lobe as the "main" or "lung" bronchus supplies the whole lung. If this part of the lower lobe trunk is obstructed, the whole lower lobe will be involved. This may happen even if only a very short stem is present. Boyden found logical for anatomic reasons to consider the "lower lobe bronchus" as the short stem which divides into superior and basal trunks. I agree with him for clinical reasons.

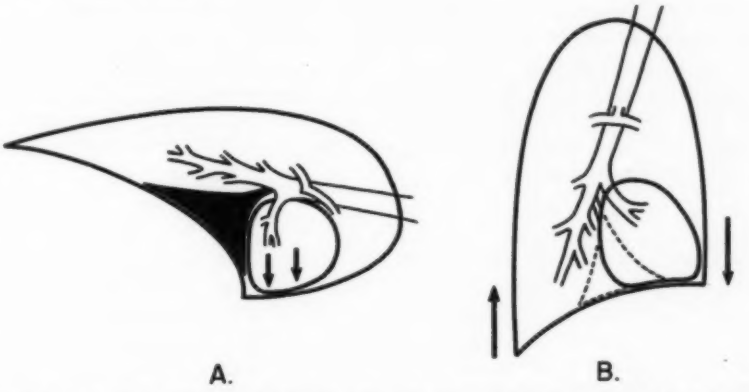

FIGURE 2: Location of the intermediate lobe in pronograde position of a dog (A) and that of the right medial basal segment in orthograde position of a man (B).

Our next obligation is to name the trunk below the superior bronchus.

I propose to name the trunk between bronchus 6 and 10 "basal stem" because there is a stem in the lower lobe and the part in question shoots off the basal segmental bronchi monopodially, and therefore, it is, in the strict meaning of the term, a "basal stem bronchus" and not only a basal trunk or common basal bronchus which are Boyden's suggestion. Its subdivisions should be described with the side-branchings as Huber proposed.

2. *The Lateral or Axillary Region of the Upper Lobes*

Clinically, the lateral or axillary region is an essential part of both upper lobes. Atelectasis, pneumonia, pulmonary abscess and tuberculous lesions (Assman focus, tuberculous cavity, epituberculosis) frequently appear in this area. The axillary territory of both upper lobes more often behaves as a pulmonary unit than some others which have been included as a segment in every nomenclature. Anatomically, it may be a subordinate district of the lung, but because of its clinical importance, I believe this subsegmental territory deserves a place in an up-to-date classification and nomenclature.

3. *Superior or Apical Segment of the Lower Lobes*

Pulmonary segment 6 is named "superior" in the Jackson-Huber nomenclature and "apical" in the London Nomenclature. It is true that the upper end of a lower lobe is more "apex-shaped" than the very apex of the lung, but the term "apex" had been applied for centuries to the highest extremity and "base" to the lowest portion of the lung. The right upper lobe rests also on a broad base, but nobody thinks of using such term as "basal segment" in the upper lobe or "apical segment" in the lower lobe. No doubt, the term "superior" is more acceptable than the "apical" for a lower lobe segment. Both Boyden and the author of this paper declined to accept this latter term.

4. *Subsuperior Segment of the Lower Lobes*

A subsuperior bronchus in the right lower lobe was observed in about 50 to 60 per cent of cases. The occurrence of this bronchus in the left lower lobe is about 8 per cent, but, if this branch cannot be found on the lobar bronchus, a similar branch appears, in almost every case, on the posterior basal bronchus. In small quadrupeds, this is a regular branch on both lower lobe bronchi. A subsuperior segmental bronchus appears frequently in bronchograms of the right lung. Because of its occurrence and clinical significance, this bronchus deserves a place in an up-to-date nomenclature.

5. *The Medial Basal Bronchus*

A medial basal district of the left lower lobe was accepted, among others, by Ewart (1889), Narath (1901), and Lucien and Weber (1936). In the Jackson-Huber nomenclature (1943), a medial basal subsegment of the left lower lobe was recognized, naming the first basal branch "antero-*medial*" basal bronchus. The committee of the London Nomenclature omitted this bronchus on the grounds of comparative anatomy. Boyden argues strongly in favor of the left cardiac region. His arguments

are: (a) Segment 7 of the left lung is equal in size to that of the right; it has merely been displaced laterally by the heart (Fig. 1); (b) the fact that the left medial and anterior basal bronchi arise from a common trunk is not a valid objection to the recognition of two segments since the same is true of the two lingular bronchi and of the left apicoposterior and anterior bronchi; (c) the medial basal component is more stable than the one whose name has been given to the whole stem; and (d) in 7 per cent the medial basal arises separately from the left lower lobe bronchus in a position comparable to that of the right medial basal. I agree with Boyden on every point. To his persuasive arguments, I can add only one more in the following paragraphs.

The committee of the London Nomenclature omitted the left medial basal bronchus and subsegment because in quadrupeds, the cardiac or intermediate lobe, which corresponds to the medial basal segment in man, appears only on the right side, and a medial branch and a lateral branch are regularly present on the anterior basal bronchus of both lower lobes (Huizinga). Similar interpretations can be found in texts on comparative anatomy. During evolution, when man advanced from

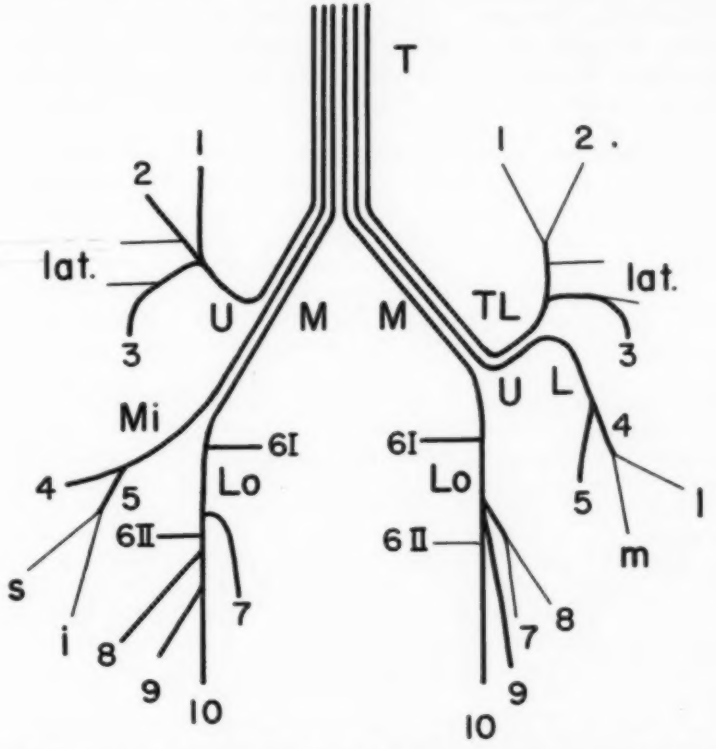

FIGURE 3: Trachea is reproduced by six parallel lines each representing a lobe. Corresponding parts of the two lungs are shown in farther branchings. T—trachea, M—main, U—upper, LO—lower, MI—middle, TL—truncated lobe bronchi, L—lingular bronchus, s—superior, i—inferior, m—medial, l—lateral; the segments are numbered. Homology of the two lungs is clearly demonstrtaed in this compilation.

the pronograde to the orthograde posture, the heart shifted toward the back and to the left, and increased the space on the right side and decreased it on the left. This circumstance gave room for the right medial basal segment, but not for the left. Therefore, a medial basal segment could develop only on the right side. I am not convinced that this is the only explanation because the problem can be judged from another, perhaps more logical, point of view. In quadrupeds, the right and left lower lobes are about equal in size. Between these two lobes, the fourth lobe of the right lung takes a middle position dorsally and caudally to the heart touching the right lower lobe directly and the left one through a pleural veil and extends ventrally between the heart and diaphragm Supplying bronchus of this lobe originates from the same site where the right medial basal bronchus arises in man.

In pronograde position, the heart rests on the ventral wall of the chest cavity and, therefore, the intermediate lobe, located dorsally and caudally to the heart, can breathe freely. During the evolution of mammals, when man assumed erect posture, the heart shifted back and was in apposition to the diaphragm; it rested directly on this lobe (Fig. 2), which jammed between the heart and diaphragm and became hindered in respiration. The lobe atrophied and, while its bronchus remained in the original location, its parenchyma joined the right lower lobe as a segment. Perhaps it is an evolutionary throwback that, in man, this segment oftener becomes an accessory lobe (cardiac lobe 35 to 38 per cent) than any other segment.

According to this view, not on the right side but on the left, there remained an empty space. To fill this space and replace the vanished left portion of the "intermediate" lobe, the medial branch of the anterior basal bronchus tended more medialwards, increased in size and filled the empty space with parenchyma. By torquation of the heart to the left, not the left lower lobe but mainly the cardiac lobe decreased in size (in quadruped), taking the form of a lingula (in man) and joined the apical lobe as the reduced intermediate lobe joined the right lower lobe.

With another example, I demonstrate the peculiar behavior of this "intermediate lobe" in quadrupeds. In the rat, the whole left lung is represented only by a single lobe which is composed by lung tissue comparable to the truncated lobe (upper division) plus the lower lobe. The intermediate lobe occupies not only the place of the left medial basal subsegment, but also that of the lingula. No lobe exists which might be analogous with the left cardiac lobe or lingula. However, a left cardiac lobe (in quadrupeds) and a lingula (in man) has been accepted in every classification for the simple reason that they exist. The left lung of many other quadrupeds has also one lobe while their right lung has four. Some of these animals are: rat, kangaroo, earth pig, mole, hedgehog, shrews (Owen)

Four other facts confirm my above-discussed theory:

a. The chest cavities and the intermediate lobe are cut into two nearly equal parts by a vertical wall similar to the mediastinum in man, separated portions on the intermediate lobe of a dog appear in both size and shape comparable to those of the medial basal segment in the right

lower lobe and medial basal subsegment in the left one of a man. They are displaced only laterally by the heart. Lateral widening of the human chest cage yields ample space for this development. In man, the latero-lateral diameter is longer than the dorso-ventral; in quadrupeds, these are reversed.

b. According to the pattern on the right side, the proper place of a left medial basal *segmental* bronchus should be on the basal stem below the superior bronchus. During evolution of man, this branch could migrate, in certain numbers of cases, from its usual location on the anterior segmental bronchus to the basal stem. Actually, Boyden found this branch on the basal stem in 7 and the author of this paper in 7.5 per cent of cases.

c. Smith found the *left medial basal subsegment* one of the "individually readily resectable" units of a lobe.

d. Embryologic studies seem to disfavor the left medial basal region. Birnbaum writes: "The space occupied on the left by the heart and pulmonary vein seems to cause an underdevelopment of one bronchial ramus, the base of the left lower lobe, thus allowing a corresponding overdevelopment on the right of the basal bronchial ramus which projects between the heart and diaphragm ('cardiac' bronchus, medial basal bronchus of the adult.)" This developmental stage imitates the situation in quadrupeds, but, in man, there is no place for a pulmonary tissue between the heart and diaphragm. Later development displaces this bronchus laterally and also gives ample space for the left lower lobe which differs slightly from the right one in both size and shape. This process also confirms my theory.

Accordingly, a left medial basal subsegment should be accepted with Jackson and Huber's terminology and with Boyden's designation: "7 + 8 medio-anterior basal segment."

6. Homology of the Two Lungs

The left upper lobe without the lingula (upper division) is the counterpart of the right upper lobe, and the lingula is that of the middle lobe. Naturally, the two lower lobes are also homologous. This correspondence was generally accepted both anatomically and clinically. However, by this classification, the pure anatomy is falsified. The left upper lobe, separated into two parts, is classified to be two distinct lobes.

The author of this paper tried to solve this controversy by naming the upper part of the left upper lobe *"truncated lobe"* and its bronchus (the upper division bronchus) *"truncated lobe bronchus."* This term means that the upper part of the left upper lobe (homologous to the right upper lobe) is accepted in segmental classification and clinical work as a lobe, but actually and anatomically it is only a part of a lobe because, in theory, the upper lobe is separated from the lingula; thus it is *truncated*. The term seems correct and it solves the controversy between pure anatomy and both accepted classification and clinical routine.

Homology of the lungs is clearly expressed in almost every segmental classification and nomenclature. With little differences, the same segments are classified in the right upper and left "truncated" lobes; in the

right middle lobe and lingula and the two lower lobes. Homologous bronchial branchings are clearly demonstrated in Fig. 3.

Segmental classification and nomenclature with the principles of Jackson and Huber might look like this:

RIGHT	LEFT
1. apical	1.-2. apicoposterolateral
2. posterolateral	
3. anterolateral	3. anterolateral
4. lateral	4. lingular superior
5. medial	5. lingular inferior
6. superior and subsuperior	6. superior and subsuperior
7. medial basal	7.-8. medioanterior basal
8. anterior basal	
9. lateral basal	9. lateral basal
10. posterior basal	10. posterior basal

SUMMARY

Six controversial and unsolved problems of bronchial classification and nomenclature are discussed. The following details of the bronchial anatomy are presented: (1) main, stem and lower lobe bronchi; (2) lateral or axillary region of the upper lobes; (3) superior or apical segment of the lower lobes; (4) subsuperior segment of the lower lobes; (5) medial basal segments, and (6) homology of the two lungs. Additional designation of bronchi, new terms, classification and nomenclature are proposed.

RESUMEN

Se discuten seis problemas que han suscitado controversia en la clasificación y la nomenclatura bronquial. Se presentan los detalles anatómicos siguientes:

(1) Bronquiolo principal y bronquio inferior; (2) Región lateral o axilar de los lóbulos superiores; (3) Segmento apical o superior de los lóbulos inferiores; (4) Segmento subsuperior de los lóbulos inferiores; (5) Segmentos mediales basales; (6) Homología de los dos pulmones. Bronquios adicionales, nuevos términos, y proposiciones sobre clasificación y nomenclature.

RESUMÉ

L'auteur discute six problèmes controversés et non résolus de classification et de nomenclature bronchiques. Les détails suivants de l'anatomie bronchique sont présentés:

(1) bronches principales, bronchopédiculaires et du lobe inférieur; (2) région latérale ou axillaire des lobes supérieurs; (3) segment supérieur ou apical des lobes inférieurs; (4) segment infra-supérieur des lobes inférieurs; (5) segments médians de la base, et (6) symétrie des deux poumons.

L'auteur propose des désignations de bronches supplémentaires, de nouveaux termes, une classification et une nomenclature.

ZUSAMMENFASSUNG

Diskussion über 6 umstrittene und ungelöste Probleme der Klassifikation und Nomenclatur des Bronchialbaumes. Es werden folgende Einzelheiten der Anatomie der Bronchien dargestellt: (1) Haupt-, Stamm- und Unterlappenbronchien; (2) laterale oder axilläre Region der Oberlappen; (3) superiores oder apikales Segment der Unterlappen; (4) subsuperiores Segment der Unterlappen; (5) mediale basale Segmente, und (6) Homologe der beiden Lungen. Es werden Klassifikationen und Nomenclatur für zusätzliche Bronchien und neue Ausdrücke vorgeschlagen.

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BLEEDING ESOPHAGEAL VARICES IN CHILDREN

Esophageal varices are an uncommon problem in children and are usually recognized with difficulty. The first clinical sign of the presence of esophageal varices in the majority of these young patients is either massive hematemesis or gross melena. This brings immediate concern to anxious parents. They in turn expect prompt medical recognition of the seriousness of the problem.

The treatment of portal hypertension is a complex and often disappointing problem. Especially in children the disadvantage of size and scarring may prevent the most usual physiologic approach, portacaval anastomosis. Should it not be feasible to do satisfactorily, a portacaval anastomosis, then the authors suggest that resection of the distal one-third of the esophagus with esophagogastric anastomosis is the treatment of choice.

Hanna, C. B., and Hastings, W. D., Jr.: "Bleeding Esophageal Varices in Children," *J. S. Carolina Med. Assoc.,* 57:226, 1961.

FUNCTIONAL STUDIES IN PULMONARY FIBROSIS

After a brief review of the pathogenesis and classification of fibroses, the authors report the results of their clinical, radiologic and functional studies of 30 patients suffering from post-tuberculous pulmonary fibrosis. They observed fibroses in various degrees of evolution: unilateral or bilateral, massive or diffuse. Massive fibrosis was limited to a zone or lobe or a whole lung. All patients showed an unchanging x-ray picture for at least two years and had normal ESR and negative sputa.

Functional tests showed that subjects with even severe pulmonary fibrosis may retain a good function of the respiratory apparatus and that an apparent discrepancy between the functional deficit and the clinical radiologic picture may exist. This diffuse fibrosis—on the contrary, massive fibrosis more or less circumscribed—gives slight x-ray change while causing remarkable functional deficit.

Mutolo, P., and Bondavalli, W.: "Il Deficit Funzionale della Fibrosi Polmonare," *Riv. Pat. Clin Tuberc.,* 34:518, 1961.

Further Investigation on the Usefulness of the Direct Qualitative Micro-Niacin Test for Distinguishing Human Tubercle Bacilli from Other Mycobacteria*

A Comparative Study of Technics Using Fresh and Stored Cultures of Varying Ages

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Interest in pulmonary disease and other infections in man caused by the so-called unclassified ("atypical") mycobacteria has been greatly intensified in recent years. Because some of these organisms are often difficult to distinguish from human tubercle bacilli and other acid-fast bacteria, investigators have been developing procedures to aid in the identification of these organisms.

In previous studies,[1-5] it was demonstrated that the aniline-cyanogen bromide, the benzidine-cyanogen bromide, and the o-tolidine-cyanogen bromide micro-niacin tests were useful for distinguishing human tubercle bacilli from other mycobacteria. Inasmuch as a limited number of strains were studied previously, it was regarded as being worthwhile to compare these tests further using larger numbers of both freshly isolated and stored organisms.

Materials and Methods

Organisms: Six hundred human-type tubercle bacilli, two bovine-type tubercle bacilli, two avian-type tubercle bacilli, 510 unclassified mycobacteria, and five saprophytic acid-fast bacilli were selected for study. The sources of some of these organisms have been indicated previously.[1,6,7] Additional strains were obtained from our stock cultures.

The human-type tubercle bacilli and the unclassified mycobacteria were isolated from various clinical specimens such as sputa, bronchial washings, gastric lavages, pleural and synovial fluids, resected lung lesions, lymph nodes, and catheterized ureteral urines. Of the 600 human-type tubercle bacilli, five strains were totally resistant to 100 mcg. of streptomycin per ml. of medium, 10 strains were totally resistant to 100 mcg. of para-aminosalicylic acid per ml., 15 strains were totally resistant to 100 mcg. of isoniazid per ml., and 20 strains were either partially or totally resistant to all three drugs in a concentration of 100 mcg. per ml. These organisms were included to determine further whether drug resistant strains would give similar reactions, with each of these niacin tests, to those of drug susceptible strains. Of the 510 unclassified mycobacteria, 206 were photochromogens, 204 were scotochromogens, and 100 were Battey types.

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**Director, Tuberculosis Research, Medical Research Laboratory, Veterans Administration Hospital.

TABLE 1—COMPARATIVE RESULTS OF THE ANILINE-CYANOGEN BROMIDE, BENZIDINE-CYANOGEN BROMIDE, AND O-TOLIDINE-CYANOGEN BROMIDE DIRECT QUALITATIVE MICRO-NIACIN TESTS AFTER INCUBATION OF CULTURES OF DIFFERENT TYPES OF MYCOBACTERIA FOR VARIOUS PERIODS ON TWEEN®-ALBUMIN NIACIN TEST MEDIUM

Number Of Cultures Tested	Test Periods: 7 Days			10 Days			14 Days			21 Days			
	Test: A-CB	B-CB	OT-CB	A-CB	B-CB	OT-CB	A-CB	B-CB	OT-CB	A-CB	B-CB	OT-BC	C
Human-Type Tubercle Bacilli													
2	D	+S	+S	D	+S	+S	+S	+S	+S	+M	+M	+M	–
2	D	+S	+S	+S	+M	+M	+M	+M	+M	+I	+I	+I	–
2	+S	D	+S	+S	D	+S	+M	+S	+M	+I	+M	+I	–
4	+M	+S	+M	+M	+S	+M	+M	+M	+M	+I	+I	+I	–
8	+M	+M	+S	+M	+M	+S	+M	+M	+M	+I	+I	+I	–
39	+S	+S	D	+M	+M	+S	+M	+M	+M	+I	+I	+I	–
86	+S	+S	+S	+S	+S	+S	+S	+S	+S	+M	+M	+M	–
457	+S	+S	+S	+S	+S	+S	+M	+M	+M	+I	+I	+I	–
Bovine-Type Tubercle Bacilli													
Copenhagen	–	–	–	+S	+S	+S	+S	+S	+S	+S	+S	+S	–
Ravenel	D	D	–	+S	+S	+S	+S	+S	+S	+S	+S	+S	–
Avian-Type Tubercle Bacilli													
Kirchberg	–	–	–	–	–	–	–	–	–	–	–	–	–
Sheard	–	–	–	–	–	–	–	–	–	–	–	–	–
Unclassified Mycobacteria													
Photochromogens													
206	–	–	–	–	–	–	–	–	–	–	–	–	–
Scotochromogens													
204	–	–	–	–	–	–	–	–	–	–	–	–	–
Battey													
70	–	–	–	–	–	–	–	–	–	–	–	–	–
Saprophytic Mycobacteria													
M. smegmatis-a	–	–	–	–	–	–	–	–	–	–	–	–	–
M. smegmatis-b	–	–	–	–	–	–	–	–	–	–	–	–	–
M. phlei-a	–	–	–	–	–	–	–	–	–	–	–	–	–
M. phlei-b	–	–	–	–	–	–	–	–	–	–	–	–	–
M. butyricum	–	–	–	–	–	–	–	–	–	–	–	–	–

A-CB = aniline-cyanogen bromide test; B-CB = benzidine-cyanogen bromide test; OT-CB=o-tolidine-cyanogen bromide test; C=controls; – = negative; D = doubtful; +S, +M, +I = slightly, moderately, and intensely positive. See methods.

Mediums and Inoculums: The Tween-albumin niacin test (TAN) medium and inoculum described previously[1] were used to perform all of the niacin tests on the freshly isolated strains. Twelve sets of the medium were inoculated with 0.3 ml. aliquots of each strain from 10 day old cultures of liquid Tween-albumin medium and placed into the 37° C. incubator in a nearly horizontal position in order to permit uniform distribution of the inoculums. Niacin tests were performed on the cultures after 7, 10, 14, and 21 days, respectively.

Both the TAN and the Löwenstein-Jensen[2] mediums were used in the tests on the stored cultures. These mediums also were inoculated with 0.3 ml. aliquots of each organism from 10 day old cultures of liquid Tween-albumin medium and incubated at 37° C. in a nearly horizontal position for three weeks. After this time, the cultures were stored at 5° C. for periods ranging from two weeks to three years.

Technics Used in Performing the Tests: The water extract method, niacin test procedures,* and controls described previously[1-4] were used. The results were read in approximately five minutes after mixing the reagents with the culture extracts, using a fluorescent light source. The results were graded arbitrarily as follows:

Aniline-Cyanogen Bromide (A-CB) Method:
− = negative, no color.
D = doubtful, questionable distinct yellow color.
+S, +M, +I = positive, distinct yellow color, reaction either slight, moderate, or intense, depending on the degree of coloration.

Benzidine-Cyanogen Bromide (B-CB) Method:
− = negative, no color, or light gray-blue color.
D = doubtful, very pale-pink color.
+S, +M, +I = positive, violet-pink color, reaction either slight, moderate, or intense, depending on the degree of coloration.

O-Tolidine-Cyanogen Bromide (OT-CB) Method:
− = negative, no color, or light blue color.
D = doubtful, dirty-blue, or very pale-pink color.
+S, +M, +I = positive, coral-red color, reaction either slight, moderate, or intense, depending on the degree of coloration.

All procedures were performed under a well-ventilated bacteriologic safety hood. Each test was repeated twice. The final readings represent average results.

Results

The data in Table 1 summarize the results of each niacin test on the freshly isolated organisms. It may be seen that all of the human-type tubercle bacilli yielded slightly to intensely positive results, whereas all of the other strains, with one exception, yielded either negative or doubtful results. It also may be seen that, as the period of incubation increased, there was a corresponding increase in both the number and degree of positive tests. When performed on cultures or human-type tubercle bacilli from seven to ten days old, the sensitivity of the tests was observed to be as follows: (1) the benzidine-cyanogen bromide and the o-tolidine-cyanogen bromide tests were slightly better than the aniline-cyanogen bromide method with four of the strains tested; (2) the aniline-cyanogen bromide and the o-tolidine-cyanogen bromide methods

*The micro-plate, micro-tube, and micro-swab tests.

TABLE 2 — COMPARATIVE RESULTS OF THE ANILINE-CYANOGEN BROMIDE, BENZIDINE-CYANOGEN BROMIDE, AND O-TOLIDINE-CYANOGEN BROMIDE DIRECT QUALITATIVE MICRO-NIACIN TESTS AFTER STORAGE OF CULTURES OF DIFFERENT TYPES OF MYCOBACTERIA FOR VARIOUS PERIODS AT 5° C.

Number Of Cultures Tested	Length Of Storage Weeks	Tests A-CB	B-CB	OT-CB	C
Human-Type Tubercle Bacilli					
2 (1)	2-3	+M	+M	+S	—
137 (12)		+M	+M	+M	—
461 (37)	4-156	+I	+I	+I	—
Bovine-Type Tubercle Bacilli					
Copenhagen					
20	5-130	+S	+S	+S	—
Ravenel					
20	10-156	+S	+S	+S	—
Avian-Type Tubercle Bacilli					
Kirchberg					
20	5-130	—	—	—	—
Sheard					
18	10-120	—	—	—	—
2	130-156	D	D	D	—
Unclassified Mycobacteria					
Photochromogens					
206	5-130	—	—	—	—
Scotochromogens					
201	10-120	—	—	—	—
3	130-156	D	D	D	—
Battey					
70	5-10	—	—	—	—
23	20-40	D	D	D	—
7	50-156	+S	+S	+S	—
Saprophytic Mycobacteria					
M. smegmatis-a					
17	5-60	—	—	—	—
3	80-130	D	D	D	—
M. phlei-b					
18	20-40	—	—	—	—
2	50-156	D	D	D	—

A-CB = aniline-cyanogen bromide test; B-CB = benzidine-cyanogen bromide test; OT-CB=o-tolidine-cyanogen bromide test; numbers in parenthesis represent strains which are either partially or totally resistant to 100 mcg. of streptomycin, para-amino salicylic acid or isoniazid per ml. of medium; C = controls; — = negative; D = doubtful; +S, +M, +I = slightly, moderately, and intensely positive. See methods.

were slightly better than the benzidine-cyanogen bromide technic with six of the strains tested; and (3) the aniline-cyanogen bromide and the benzidine-cyanogen bromide procedures were slightly better than the o-tolidine-cyanogen bromide test with 47 of the strains tested. When used on the cultures of human-type tubercle bacilli from 14 to 21 days old, however, the sensitivity of all three niacin tests was virtually the same.

The data in Table 2 summarize the results of each niacin test on the stored cultures. It also may been seen that all of the human-type tubercle bacilli gave slightly to intensely positive reactions. These results were observed irrespective of the period of storage or the dryness of the cultures. The drug resistant organisms yielded similar results to those of the drug susceptible strains. With two exceptions, all of the other mycobacteria yielded either negative or doubtful results. In the bovine group of tubercle bacilli, all of the cultures exhibited slightly positive results

at each test period. In the Battey group of organisms, seven out of a total of 100 cultures yielded slightly positive results within the 50 to 156 week test periods.

That the niacin content of human-type tubercle bacilli increases with the age of cultures incubated at 37° C. has been observed previously.[1,2,4,9,10] From the present, as well as other observations,[3,5,11] the same conditions apparently result at 5° C., not only for human-type tubercle bacilli, but also in a number of instances, for some of the Battey organisms. However, the additional niacin produced at 5° C., even after long storage, is considerably less than at 37° C. because of the reduced metabolism of the organisms.

The sensitivity of each niacin test under these conditions was virtually the same.

SUMMARY

The study described here was undertaken to compare further three recently reported micro-niacin tests using both freshly isolated and stored cultures of various types of mycobacteria.

When performed on the fresh cultures, it was observed that all of the human-type tubercle bacilli yielded slightly to intensely positive tests, whereas, all of the other strains, with two exceptions, gave either negative or doubtful results. As the period of incubation increased, there was a corresponding increase in both the number and degree of positive results. The bovine-type tubercle bacilli exhibited slightly positive results with each test after the 10, 14, and 21 day periods, respectively.

When used on cultures of human-type tubercle bacilli from seven to ten days old, the sensitivity of the tests was observed to be as follows: (1) the benzidine-cyanogen bromide and the o-tolidine-cyanogen bromide tests were slightly better than the aniline-cyanogen bromide method with four of the strains tested; (2) the aniline-cyanogen bromide and the o-tolidine-cyanogen bromide methods were slightly better than the benzidine-cyanogen bromide technic with six of the strains tested; and (3) the aniline-cyanogen bromide and the benzidine-cyanogen bromide procedures were slightly better than the o-tolidine-cyanogen bromide test with 47 of the strains tested. When used on the cultures of human-type tubercle bacilli from 14 to 21 days old, however, the sensitivity of all three niacin tests was virtually the same.

When performed on the stored cultures, it also was observed that all of the human type tubercle bacilli exhibited slightly to intensely positive results irrespective of the period of storage or the dryness of the cultures. The drug resistant organisms yielded similar results to those of the drug susceptible strains. With two exceptions, all of the other mycobacteria exhibited either negative or doubtful tests. In the bovine group of tubercle bacilli, all of the cultures yielded slightly positive results at each test period. In the Battey group of organisms, 7 out of 100 cultures exhibited slightly positive results within the 50 to 156 week test periods. The sensitivity of each niacin test under these conditions was virtually the same.

The tests are simple, efficient, safe, and economical. Reproducible and consistent results can be obtained on cultures as old as three years. In most instances, the results exhibited by human tubercle bacilli are sufficiently different in character from the results produced by other mycobacteria to enable a clear-cut differentiation of these organisms. For greater effectiveness, it is recommended that the niacin test be used in conjunction with other differential procedures.

RESUMEN

Se emprendió este estudio para comparar tres pruebas de microniacina recientemente relatadas, usando cultivos recien aislados, así como cultivos almacenados de varios tipos de micobacterias.

Cuando se llevaron a cabo en cultivos recientes se observó que todos los cultivos de tipo humano rindieron desde ligeramente positivos hasta intensamente positivos, en tanto que todas las otras cepas, con dos excepciones, dieron ya sea negativos o dudosos. Cuando el periodo de incubación aumentaba había un aumento correspondiente del número y del grado de los resultados positivos. El tipo bovino mostró reacción después de 10, 14 y 21 días respectivamente.

Cuando se usaron estas pruebas en cultivos de tipo humano de 7 a 10 días de edad, la sensibilidad se observó como sigue: (1) las pruebas de bromuro de bencidina-cianógeno y la de bromuro de o-tolidina-cianógeno, fueron ligeramente mejores que la técnica de bromuro de anilina-cianógeno con cuatro de las cepas probadas; (2) los métodos de anilina cianógeno (bromuro) y la o-tolidina-cianógeno (bromuro de) fueron ligeramente mejores que la del bromuro de benzidina-cianógeno con seis de las cepas probadas; y (3) el bromuro de anilina-cianógeno y el bromuro de bencidina cianógeno fueron ligeramente superiores a la o-tolidina-cianógeno-bromuro, con 47 de las cepas probadas.

Cuando se usaron en cultivos de bacilos tipo humano de 14 a 21 días de edad, sin embargo, la sensibilidad de las tres reacciones fue virtualmente la misma.

Cuando se llevaron a cabo en cultivos almacenados se observó que todos los bacilos de tipo humano mostraron desde ligeros hasta intensos resultados positivos, cualquiera que fuera el periodo de almacenamiento y la sequedad de los cultivos. Los organismos drogo-resistentes rindieron resultados semejantes a los de los drogosensiblees. Con nueve excepcionees, todos los demás bacilos mostraron preubas negativas o dudosas. En el tipo bovino de bacilos tuberculosos, todos lo3 cultivos dieron resultados ligeramente positivos en cada periodo de pruebas. En grupo Battey, 7 de 100 cultivos dieron resultados ligeramente positivos dentro de los periodos de 50 a 156 semanas de pruebas. La sensibilidad de cada reacción de la niacina bajo estas circumstancias fue virtualmente la misma.

Las reacciones son simples, eficientes, seguras y económicas. Se pueden obtener resultados reproducibles en cultivos tan viejos como de tres años. En el mayoría de los casos, los resultados mostrados por el bacilo humano son suficientemente distintos de los resultados que dan otras micobacterias, para permitir una clara diferenciación de estos organismos. Para una efectividad mayor se recomienda que la reacción de la niacina se use en conjunción con otros procedimientos diferenciales.

ZUSAMMENFASSUNG

Die hier vorgelegte Untersuchung hatte zum Ziel, weitere Vergleiche anzustellen mit drei Mikro-Niacin-Proben, über die kürzlich berichtet worden war, unter Verwendung von frisch gewonnenen, als auch längere Zeit gelagerten Kulturen verschiedener Arten von Mycrobakterien.

Bei der Vornahme an den frischesten Kulturen wurde festgestellt, daß alle humanen Typen der Tuberkelbazillen schwache bis intensive positive Teste ergaben, während alle anderen Stämme mit 2 Ausnahmen entweder negativ oder zweifelhaft ausfielen. In dem Maße, wie die Inkubationsperiode anstieg, zeigte sich ein entsprechender Anstieg sowohl in der Zahl als auch der Stärke positiver Resultate. Der bovine Typ der Tuberkelbazillen brachte leicht positive Ergebnisse mit jedem Test nach 10 —, bzw. 14 — und 21 — tägigen Zeitabschnitten.

Bei Benutzung von 7 — 10 Tage alten Kulturen von humanen Typen der Tuberkelbezillen wurden folgende Empfindlichkeiten der Teste ermittelt: 1.) der Benzidin-Cyan-Bromtest und der Tolidin-Cyan-Bromtest waren etwas besser als der Anilin-Cyan-Bromtest bei 4 der geprüften Stämme 2.) der Anilin-Cyan-Bromtest und der Tolidin-Cyan-Bromtest waren etwas besser als die Benzidin-Cyan-Bromtechink bei 6 der geprüften Stämme; 3.) die Anilin-Cyan-Bromidmethode und die Benzidin-Cyan-Brommethode waren etwas besser als die Tolidin-Cyan-Brommethode bei 47 der geprüften Stämme. Bei Benutzung der 14 bis 21 Tage alten Kulturen menschlicher Typen von Tuberkelbazillen war jedoch die Empfindlichkeit aller drei Niazin-Teste im wesentlichen die gleichen.

Wurden gelagerte Kulturen gebraucht, so wurde auch beobachtet, daß alle humanen Type von Tuberkelbazillen zu leichten bis stark positiven Resultaten führten-unbeschadet der Dauer der Aufbewahrung oder der Trockenheit der Kulturen. Die resistenten Organismen ergaben ähnliche Resultate wie diejenigen bei senaiblen Stämmen. Mit 9 Ausnahmen ergaben alle anderen Mycobakterien entweder negative oder zweifelhafte Proben. In der Gruppe der bovinen Typen der Tuberkelbazillen erbrachten alle Kulturen schwach positive Resultate bei jedem Testabschnitt. Die Organismen der Battey-Gruppe zeigten in 7 von 100 Kulturen leicht positive Resultate innerhalb der 50 — 156— wöchigen Testperioden.

Die Empfindlichkeit eines jeden Myacin-Testes war unter diesen Bedingungen im wesentlichen die gleiche.

Die Proben sind einfach, wirksam, sicher und wirtschaftlich. Immer wieder zu reproduzierende und gleichmässige Resultate kann man selbst an 3 Jahre alten Kulturen erreichen. In den meisten Fällen sind die mit dem humanen Tuberkelbazillen gewonnenen Resultate im Charakter genügend verschieden, von den von den anderen Mycobakterien bewirkten Ergebnissen, um eine ganz klare Differenzierung dieser Organismen zu gestatten. Zur Steigerung der Wirksamkeit wird empfohlen, den Niacintest in Verbindung mit anderen Differenzierungsverfahren zu benutzen.

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THE EFFECT OF ANTIBIOTICS ON THE TOXIN PRODUCTION OF *STAPHYLOCOCCUS AUREUS*

The effects of six antibiotics on the growth and alpha toxin production of an antibiotic-susceptible strain of *Staph. aureus* were studied. The amount of inhibition of toxin production by chloramphenicol, tetracycline, oxytetracycline, and oleandomycin was found to be directly proportional to the amount of inhibition of growth.

Streptomycin and bacitracin were shown to inhibit toxin production to a degree significantly out of proportion to the amount of inhibition of growth. The absolute effect of a given dose of streptomycin or bacitracin was found to be increased by the addition of chloramphenicol. However, the relative effect of the combination on toxin production, when compared to the effect on growth, was found to be less than that observed when streptomycin or bacitracin acted alone.

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PHYSICAL EXERCISE AS A FACTOR IN REHABILITATION OF TUBERCULOUS PATIENTS

The influence of physical exercise in the form of gymnastics, rhythmic exercise with the accompaniment of music, sports and games, on the physical re-education in tuberculosis patients was investigated. Clinical and pulmonary function tests were carried out in two groups of tuberculous convalescents with the lesions classified as stabilized.

Group I included 95 patients; gymnastic exercises were carried out every day for ten minutes daily, rhythmic exercises for 45 minutes daily twice weekly and light sports for a period of eight months. Group II included 17 patients: rhythmic exercises were done every day for 45 minutes for about two months, in addition to gymnastics done every day.

Pulmonary function tests and clinical examination were done in both groups. The findings indicate the possibility of improvement of respiratory function and of increase of exercise tolerance, as well as correction and improvement of fitness by means of exercise. No exacerbation of pulmonary lesion is to be feared, provided the exercises are carefully graded and antimicrobial drugs are administered. The patient is kept under strict medical care and radiologic examinations and pulmonary function tests are carried out frequently.

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Papworth and Enham-Alamein Village Settlements

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Papworth Village Settlement was founded by Sir Pendrill Varrier-Jones in 1918. His ideas on the proper after-care of the tuberculous were already formed in 1916 when he opened two cottages and a small workshop at the village of Bourn about five miles from the present site of the Settlement. He was convinced that sanatorium treatment as then carried out was but a half-way house to death for all but the earliest forms of the disease; it was a regime with a good middle, but with bad support at both ends. The vast majority of patients had at best moderately-advanced disease at the time of admission; Marcus Paterson used to say that the most dangerous journey in the world was the 30 miles between London and Frimley, as the patient got on the train with early disease and got off with advanced disease. The true significance of physical signs were not then understood; it was only much later, with the improvement in technique and interpretation of x-ray film examination by such pioneers as Stanley Melville, that it was realized that crepitations at the apex meant that at least one third of the lung was involved and that crepitations found below the collarbone meant disease of at least half of the lung. Even if the patient improved or remained in a static condition during his residence in the sanatorium, his outlook was grave; 66 per cent of all with more than early disease died within five years of discharge, and the conversion of positive to negative sputum during residence made but little difference in prognosis.

Varrier-Jones saw that the one hope lay in the continuance of sanatorium conditions after discharge; the patient must have sheltered living conditions and sheltered work. He shocked his fellow tuberculosis physicians by saying that the patient could in such conditions live with his family, provided that he applied rigidly in his home the lessons of sanatorium hygiene. The prophets of disaster to the Village children were confounded; no child contracted tuberculosis, as happened then and still happens in the homes of the tuberculous, nor did they break down when they left home for open employment. In spite of the fact that the majority of the Village boys who served in the Army in World War II were captured at Singapore and served on the Death Railway in Siam, no Papworth young man returned home with tuberculosis, which is a remarkable record to those of us who saw the appalling results in young men who had joined the Forces from supposedly normal homes and went through the same ordeal.

By 1934, Papworth was employing all known modern methods of collapse therapy. It had the latest surgical unit, and employed some of the best thoracic surgeons then working in London. Its results were impressive.

The experience of Papworth during World War II did much to overcome the cruel ostracism of the tuberculous, for the workshops had to extend rapidly to comply with the Essential Works Order under which 500 extra, supposedly fit, workers had to be employed. Over the period

of five years, only two of them developed tuberculosis, and both were contacts with patients outside the Settlement who were known to have positive sputum.

The introduction of the Ministry of Labour Training Scheme for the tuberculous in 1948 provided the necessary bridge over the gap between treatment and after-care which resulted from the introduction of the National Health Act. Generous allowances were provided for the patient-worker and his family. Under this scheme, the Ministry of Health became responsible, through the East Anglian Regional Board, for treatment until the patient had reached fitness for five hours work a day, while after-care following colonization became the responsibility of the local authority of domicile. The Settlement was able therefore to continue much on the lines on which it had worked prior to the appointed day in July, 1948, when the new Act came into operation. Proper placement after training was ensured by close cooperation between the Disablement Resettlement Officer of the patient's domicile, the social worker of Papworth and the D.R.O. of Cambridge.

Between 1948 and 1955, 342 trainees had left with satisfactory results. Some left the Settlement for various reasons, mainly domestic, when they were fit to work only three hours a day; nevertheless, 76 per cent of them were fully fit in 1955, and 51 per cent of them were at full work. The record of those who left fit to do six hours' work per day was substantially better; 87 per cent reported themselves as fit, and 77 per cent were at full work. The benefit of colonization was shown in the result of 90 per cent fit, all at full work.

The Village has now 270 houses and flats, with some 800 residents, including the wives and children of settlers. In addition, there are 175 colonists in hostels, some of them married men waiting for accommodation in the Village. The Industries employ over 500 men and women in printing and bookbinding, woodworking, leather and metal working, including the building of such vehicles as fire engines and television vans, and in upholstery. Several of the workers are the wives and children of settlers; the Industries are recognized for apprenticeship under trade union rules, so that the boys need not leave home before reaching the stage of journeymen in their chosen trades.

On admission, the trainee-worker enters an initial training school to learn the tools and materials of his trade which he can choose within the limits of known work-vacancies in his home town, as detailed by his local D.R.O. He then passes to the workshops where he follows strict schedules laid down by the Ministry of Labour, whose visiting officials, with our own executives and social worker, assess his progress until he arrives at the stage of the minimum requirements for employment under trade union regulations. He is then placed in work near his own home through his local D.R.O.

Should he express a desire to settle, and medical opinion considers he has a better opportunity to remain fit with the prospect of security and quarters we can offer, he is paid as agreed with the union of his trade, at two-pence per hour under the full rate in open industry. He adds one half-penny per hour for every year of service so that in four years he commands the full rate paid to workers in open industry.

Whether married or single, he lives in a hostel; a married man has his name placed on a waiting list for a Village house to which he can in due course bring his wife and family. As the estate is not run on a profit basis, low rentals allow ample means for the proper support of the family which may enjoy the many Village amenities such as the dramatic, social, dancing, football, boxing and tennis clubs. There is a Village school for the children until the age of 12, and we have an Anglican Church and Roman Catholic and Methodist Chapels.

Enham Village Centre owes its inception in 1918 to the late Field-Marshal Lord Birdwood, who had a great interest in disabled ex-servicemen, to whom admission was restricted. All forms of disability except pulmonary tuberculosis were then catered for. The Industries had to be confined almost entirely to woodworking. As it was a voluntary institution and interest in the welfare of ex-servicemen fell away within a comparatively short time, the Centre was not in a good way economically by 1927. The Governors therefore approached Sir Pendrill Varrier-Jones and asked him to direct it in conjunction with Papworth; one result was that it shared in the increased work under the Essential Works Order from the outbreak of World War II.

In 1946, with the winding up of the Officers' Club in Cairo, an Alamein Fund was formed. Several projects that might be of use to ex-servicemen were considered and it was finally decided that the money should be spent by adding to the equipment and hostel and housing accommodation of Enham Centre, which then became the Enham-Alamein Village Centre. Admissions supported by the Fund were to be confined to men suffering from pulmonary tuberculosis, with priority for former Eighth Army men. A new hostel was opened by Her Royal Highness the Princess Royal on Alamein Day, 1950. The Ministry of Labour then allowed the Centre to share in the training scheme for the tuberculous which had then been in operation for two years at Papworth. It was soon found, however, that the number of ex-service applicants was falling, and it was decided that civilian sufferers from the disease could be admitted, with priority for ex-servicemen, particularly in the matter of settlement and housing in the Village.

The Centre now has 150 houses, bungalows and flats. Its Industries, which have some 230 colonists and trainees, consist of woodworking of all forms, upholstery and light engineering. Recently, the governing body has built and equipped the first shop in the category of sheltered workshop as defined by the Ministry of Labour.

Papworth and Enham-Alamein are separate in their economy; each has its voluntary management body. They are, however, combined in policy through a Central Controlling Committee with H.R.H. the Princess Royal as President, the Dowager Marchioness of Linlithgow as Vice-President, and Lord Tedder as Chairman, and they share the same senior executives in the industrial director, accountant, appeals secretary and medical director.

Since 1948, there has been a marked fall in the interest in the rehabilitation of the tuberculous. The reasons are not far to seek, the main one being loss of fear of the disease. The introduction of the National Health Act in that year coincided with the widespread use throughout the

country of streptomycin; since then the number of deaths has fallen steadily. In 1920, shortly after the establishment of Papworth, the figure for England and Wales was 38,775. By 1948 we had already returned to the improved position that occurred between the two World Wars: the figure had fallen to 19,088. By 1958, however, it was only 4,000. There has been a similar trend in notifications of new cases. In 1920, the figure was 73,372; in 1948, 52,576; in 1958, it had fallen to 28,860: in other words, since the institution of Papworth, the fall has been in the neighborhood of 66 per cent.

The Settlements attracted the vast majority of applicants for admission from sanatoria. The falling away in waiting lists for sanatoria, shown in the closure of a large number throughout the country, has had its effect. More and better housing, with resulting betterment in home hygiene, has led to an increasing number of the tuberculous who continue work while under treatment at chest clinics; some 350,000 are now on the clinic registers of England and Wales. Most recent applicants for admission suffer from advanced disease, and are severely disabled. They are beyond help from any form of surgical treatment and have positive sputum that has resisted every known antibiotic. Many are homeless and of the type that has never worked, and many have psychologic difficulties that have necessitated treatment in mental institutions. They are therefore unfit for training, and their introduction to the Settlement would lay the children of our Villages open to a type of disease for which we have no present answer.

In 1954, it became evident to the Committees of Management of the Settlements that steps should be taken for the adaptation of part of their equipment to the training and colonizaion of sufferers from nontuberculous disabilities, and it was decided that Enham-Alamein should embark on a pilot scheme. Therefore, negotiations were begun with the County Councils Association, the London County Council and Welfare Authorities throughout the country for the establishment of two schemes, one for men who might be fitted for return to open industry, the other for those so severely disabled as to require residence and sheltered workshop conditions. Both deal with sufferers from locomotor disabilities, for example; those resulting from arthritis, poliomyelitis and paraplegia. Sufferers from cardiac disease and from chest conditions such as chronic bronchitis and bronchiectasis are also included.

The introduction of such schemes at Enham-Alamein meant that we could no longer admit patient-workers with positive sputum. Those who have sputum negative to culture examination for at least three months before the date of application can, however, be accepted; they can have the full benefits of the Ministry of Labour Training Scheme for the tuberculous.

The Ministry of Labour generously offered a new scheme of training. All nontuberculous patient-workers, ex-service or civilian, who are fit to enter our present workshops, can enjoy one year's training with financial support. The aim is to return them to open industry, unless they are found at the end of training to require continued sheltered conditions, in which case they can be colonized on the same lines as are open to the tuberculous.

The second scheme applies to men who require help under what is known as "Part III-Accommodation." These are unfortunate sufferers from such conditions as spastic disease, unfit for open employment; in other words, they are beyond category II of the disabled as defined by the Ministry of Labour. Their workshop is in the accepted term a sheltered workshop, with its own economy. On admission they are supported by the Welfare Authorities of their place of domicile. If they reach fitness for a 30-hour week, they become wage-earners under rules agreed with the trade unions. As they can never become economic, we are allowed to apply to the Ministry of Labour for part of our losses under the terms of the deficiency grants for sheltered workshops.

Our first sheltered shop is equipped for making unlined note-books. Paper cutting is done by electrically driven guillotines with fool-proof safety devices. As the experience and ability of the workers increase, we shall set up simple line-printing and binding machines; at present such finishing processes are carried out at Papworth. The number of applicants under both schemes is increasing so that we shall have to extend our industries and our hostels and housing. It is our hope that some of the severely disabled will make such progress that they can be placed at work in our usual shops through the fitting of machine adaptations designed by our visiting consultants in rehabilitation. Through these consultants, and by arrangement with the Regional Board, assessment of ability to work and any necessary intercurrent treatment for unstable disabilities can be carried out at the Royal Hampshire Hospital, Winchester, or the Odstock Unit, Salisbury, but we hope to have shortly our own local unit. The next step will be to make arrangements for the admission of women.

Papworth is now proceeding on the same lines. No colonist, married or single, has now a positive sputum, and in order to comply with Ministry of Labour and public health requirements on the training of men and women with nontuberculous disabilities the Committee has decided that future admission of the tuberculous must be confined to those with sputum negative to culture examination. Other adaptations will follow in due course, so that the facilities and long experience of the Settlement can be open to an increasing number of disabled men and women in every category.

DIAGNOSIS OF PLEURAL EFFUSION

Seventy consecutive cases of idiopathic pleural effusion admitted to Sarojini Naidu Hospital, Agra, were invested. A definite etiologic diagnosis could be established in 40 cases (57 per cent). These included tuberculous effusion (20 cases), malignant disease of pleura (10 cases) and pyogenic effusion (1 case). Pleural biopsy proved to be the most helpful of all the diagnostic aids in elucidating the etiology of tuberculous pleural effusion as it gave positive results in 40 per cent of cases against 24.4 per cent positive results with fluoroscopic, sputum and pleural fluid examinations. In the group of malignant effusions, malignant cells were found in pleural fluid much more often (46.4 per cent) than by pleural biopsy which was positive in 33 per cent of cases.

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Ventilation Studies in Nonsmokers and Smokers*

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Since the earliest use of tobacco in Western cultures, there has been considerable interest in the potentially harmful effects of tobacco smoke on the respiratory tract. Recent approaches to the subject include: (1) epidemiologic and pathologic studies supporting the view that chronic inhalation of tobacco smoke may be associated with the development of lung cancer;[1-3] (2) epidemiologic data that show a greater prevalence of chronic bronchitis and pulmonary emphysema in cigarette smokers than in nonsmokers;[4-6] (3) physiologic studies which demonstrate that inhalation of cigarette smoke is associated with an acute rise in expiratory airway resistance in persons with pulmonary emphysema[7,8] and a significant decrease in airway conductance (the reciprocal of resistance) in normal subjects.[9]

Ample evidence is available that tobacco smoke can cause local changes throughout the respiratory tract, including hyperemia and other signs of inflammation and hypersecretion by mucus producing glands. It is not surprising that these and possibly other changes may be reflected by

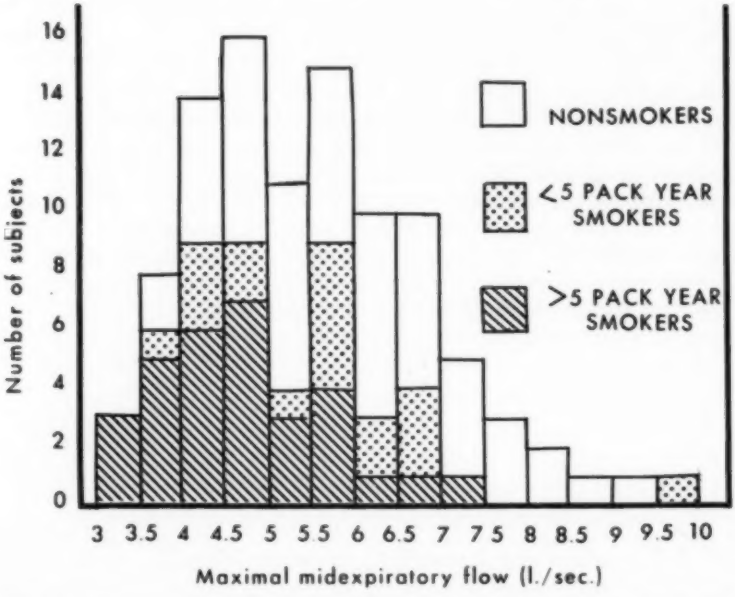

FIGURE 1: Frequency distribution of maximal midexpiratory flow rates in 98 men ages 20 to 29, grouped according to duration-intensity of cigarette smoking.

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physiologic tests which provide information regarding the functional state of the airways.

A commonly accepted method of assessing some of the properties of the airways is to determine the volume-time relationship during a forced expiration. The maximal midexpiratory flow (MMF) described by Leuallen and Fowler in 1955[18] is a sensitive, simple means for detecting impairment of airflow during a forced expiration. The MMF describes the mean flow rate (in liters per second) during the middle half of a forced expiration and has been found to be a more sensitive index of airflow impairment than the maximum breathing capacity or the 1 second or 3 second per cent of the vital capacity.[19]

The purpose of the study described below was to determine whether or not maximal midexpiratory flow rates differed significantly in nonsmokers and cigarette smokers.

Material and Methods

Three groups of volunteers were studied. Subjects were classified according to the number of pack-years they had smoked cigarettes, a pack-year being defined as the smoking of 20 cigarettes (one pack) daily for one year.

Group 1 was composed of 98 young medical students, hospital employees and physicians ages 20 to 29. All were in apparent good health; none had asthma or other respiratory disease. The group was divided into lifelong nonsmokers (NS), those who had smoked less than five pack years (<5 PYS), and those who had smoked five or more pack years (>5 PYS).

Group 2 consisted of 84 bank employees all over age 40. Some had respiratory symptoms including chronic cough, expectoration and exertional dyspnea. Subgroups included lifelong nonsmokers (NS), men who had smoked less than 20 pack years (<20 PYS), and those who had smoked more than 20 pack years (>20 PYS).

Group 3 consisted of 78 women over age 40 employed in a bank, some of whom had respiratory symptoms. Subgroups were the same as in Group 2.

Age, sex, height, weight and smoking habits were recorded for each subject and are summarized in Table 1. No attempt was made to have smokers abstain from smoking on the day of the test. Subjects in Group 1 made a complete, slow expiration into a 9 liter Stead-Wells spirometer

TABLE 1—PHYSICAL CHARACTERISTICS OF NONSMOKERS AND SMOKERS

Group	No.	Mean Age	Mean Ht.	Mean Wt.	Mean Pack Years
1 NS	49	23	177 cm.	165 lbs.	0
<5PYS	18	21	177 cm.	162 lbs.	2.5
>5PYS	31	24	180 cm.	151 lbs.	7.4
2 NS	14	56	179 cm.	177 lbs.	0
<20PYS	17	52	175 cm.	160 lbs.	9.0
>20PYS	53	56	177 cm.	168 lbs.	>20
3 NS	39	51	161 cm.	139 lbs.	0
<20PYS	17	52	163 cm.	125 lbs.	6.6
>20PYS	22	49	163 cm.	130 lbs.	>20

and a tracing of this was recorded. In all subjects, a rapid, forced expiration was recorded on a kymograph moving at a speed of 32 mm./sec. After a few moments rest, the procedure was repeated until three acceptable tracings had been obtained.

Volumes were converted to BTPS and for all subjects the maximal midexpiratory flow (MMF) was determined. The largest MMF value in an individual was the one reported. In Group 1 the largest 1 second volume ($F.E.V._1$) was expressed as a percentage of the largest vital capacity. In persons in Groups 2 and 3, the largest 1 second volume was multiplied by a factor of 40 and called the indirect maximum breathing capacity (indirect MBC).

The formula used for the predicted maximum breathing capacity in men was that of Wright,

$$MBC = \text{ht. in cm.} \times (1.24 - 0.0095 \times \text{age})$$

and for women that of Cournand (modified by addition of 20 per cent),

$$MBC = (71.3 - [0.474 \times \text{age}]) \times 1.2 \times B.S.A.$$

Results

Data contrasting ventilatory performance in nonsmokers and smokers are presented in Table 2.

In Group 1 (young men), the difference between the mean MMF of the nonsmokers and the 5-plus pack-year smokers is highly significant ($p<.001$). The difference between the mean MMF of the nonsmokers and those who smoked less than 5 pack-years is not significant. The difference between the less than 5 and the more than 5 pack-year smokers is significant ($.02<p<.05$). The mean 1 second vital capacity does not differ significantly in the subgroups of Group 1.

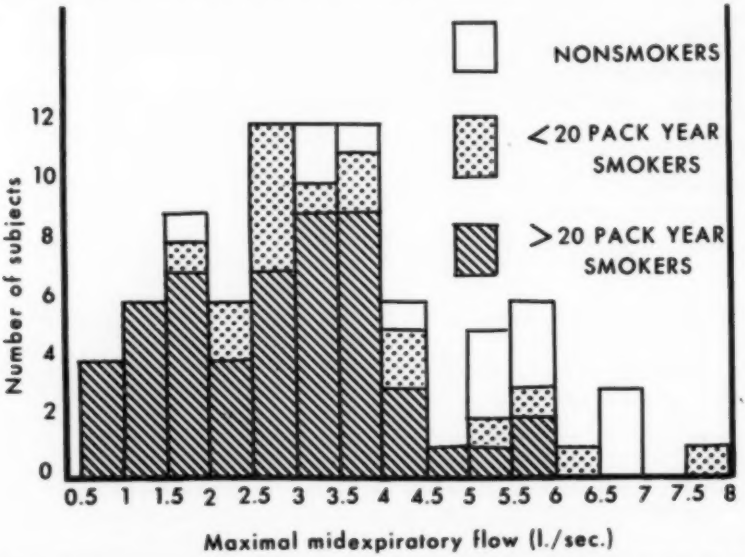

FIGURE 2: Frequency distribution of maximal midexpiratory flow rates in 84 men over 40 years of age, grouped according to duration-intensity of cigarette smoking.

TABLE 2—VENTILATORY DATA IN NONSMOKERS AND SMOKERS

Group	Smoking Class	Mean MMF (L./Sec.)	Mean 1 Sec. VC (% of VC)	Mean Indirect MBC (% of Predicted)
1	NS	5.98±1.37	83%±7	
young	<5 PYS	5.67±1.36	81%±6	——
men	>5 PYS	4.74±0.94	80%±7	
2	NS	4.98±1.48		98%±16
men	<20 PYS	3.40±1.21	——	96%±16
over 40	<20 PYS	2.86±1.37		81%±16
3	NS	3.16±0.94		92%±15
women	>20 PYS	3.06±0.84	——	97%±11
over 40	>20 PYS	2.98±1.38		95%±15

In Group 2 (men over 40), the difference between both the mean MMF and mean indirect MBC of the nonsmokers and the cigarette smokers is significant ($p<.001$).

In Group 3 (women over 40), differences in mean MMF and mean indirect MBC in nonsmokers and both groups of smokers are not significant.

The frequency distribution of maximal midexpiratory flow rates in Groups 1, 2 and 3 are shown in Figures 1, 2 and 3 respectively.

Discussion

The finding of significant differences in ventilatory performance in comparably-aged groups of nonsmoking men over 40 and men who have smoked for a number of years is not altogether surprising. Chronic bronchitis and pulmonary emphysema are much more common in persons who have smoked cigarettes for many years than in nonsmokers. The ventilatory defects that accompany these diseases are well known. If

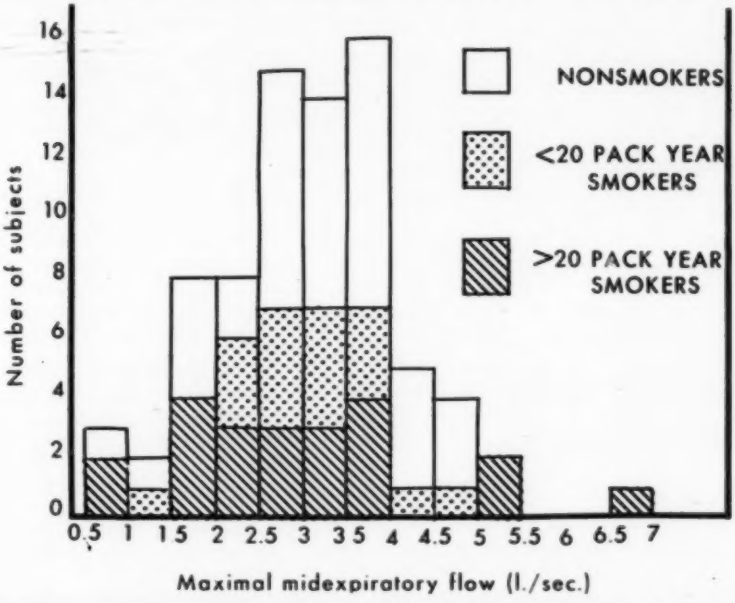

FIGURE 3: Frequency distribution of maximal midexpiratory flow rates in 78 women over 40 years of age, grouped according to duration-intensity of cigarette smoking.

smoking adversely affects the airways, differences in ventilatory performance might be expected when nonsmokers and smokers are compared. The biological significance of the differences observed in the present study can be interpreted only in the light of more complete respiratory investigations.

A difference between the mean MMF of young men nonsmokers and the mean MMF of 5 plus pack-year smokers suggests that airway changes may occur within a short time after beginning smoking. The failure of the mean 1 second vital capacity to differ significantly in the young men of the present study confirms the finding of McKee[11] and tends to substantiate the view that the maximal midexpiratory flow is a more sensitive measurement than the 1 second vital capacity (expressed as a per cent of the vital capacity).

The absence of significant differences in ventilatory performance in women nonsmokers and smokers in this study calls attention to the possibility that men and women may react differently when exposed to respiratory irritants.

SUMMARY

The maximal midexpiratory flow rate was found to be significantly greater in nonsmoking men than in men who had smoked cigarettes for at least 5 pack-years. No significant difference between women nonsmokers and smokers was observed.

RESUMEN

El flujo expiratorio máximo medio espiratorio, se encontró significantemente mayor en los no fumadores que en los hombres que han fumado por lo menos durante 5 años. No hay diferencia significativa entre las mujeres fumadoras o no.

RESUMÉ

Le taux du débit expiratoire maximum fut trouvé être nettement plus élevé chez des hommes non fumeurs que chez des hommes qui avaient fumé des cigarettes pendant au moins cinq années. Il n'y eut aucune différence nette entre les femmes non fumeurs et les autres.

ZUSAMMENFASSUNG

Die maximale mitte-Expirationsluft wurde als beträchtlich höher ermittelt bei Männern, die nicht rauchten, als bei Männern die mindestens 5 Päckhen Zigaretten pro Jahr geraucht hatten. Ein wesentlicher Unterschied bei Frauen, die rauchten, gegenüber solchen, die nicht rauchten, wurde nicht beobachtet.

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Spontaneous Pneumothorax: A Review of 71 Cases

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Spontaneous pneumothorax is generally described as pneumothorax occurring in an apparently healthy individual without antecedent history of pulmonary disease or trauma. In most instances, it is a benign, self-limiting condition with full recovery following bed rest alone. Because of the long morbidity and the high incidence of recurrence associated with conservative methods of treatment, more vigorous modes of therapy have been advocated and employed. This paper is a review of 71 cases of spontaneous pneumothorax that have been treated at the San Francisco Veterans Administration hospital over the 12-year period from June, 1947 through June, 1959.

Etiology

For many years spontaneous pneumothorax was considered pathognomonic of pulmonary tuberculosis. From 60 to 90 per cent of cases were attributed to this disease. Kjaergaard, in 1932, was the first to report that the incidence of spontaneous pneumothorax was no greater among patients with tuberculosis than it was in the general population. Since that time numerous investigators have reported similar findings.[a] It is now recognized that most cases of spontaneous pneumothorax are secondary to the rupture of congenital or acquired subpleurål blebs with the escape of air into the pleural space or into mediastinal structures. It may occur as a complication of infectious processes, such as pneumonia or tuberculosis. It is occasionally encountered in patients with either primary or secondary pulmonary neoplastic processes. It is not infrequently seen in traumatic injuries of the thoracic cage.

Material

Over the 12-year period from June, 1947 through June, 1959, 67 patients were treated at the San Francisco Veterans Administration Hospital for 71 episodes of spontaneous pneumothorax. Not all were the so-called simple or idiopathic type. However, all are included in this review since various modes of therapy used at this facility are being evaluated.

From Table 1, it is seen that of the 71 cases, associated pulmonary conditions were present in 15 patients, as determined by the history, physical examination, or by x-ray film studies. Of the remaining 56, pleural blebs were demonstrated at thoracoscopy or thoracotomy in 13. In the absence of other positive findings, rupture of a pleural bleb was assumed to be the etiology in the remaining 43 patients.

Clinical Features

Age: All of the patients in this series were men ranging from 19 to 77 years of age. Seventy per cent were between 19 and 40 years.

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TABLE 1—71 CASES OF SPONTANEOUS PNEUMOTHORAX

Associated Pulmonary Conditions:		
None identified *(pleural blebs assumed)*	43	
Pleural blebs demonstrated by thoracoscopy or thoracotomy	13	56
Emphysema, marked	5	
Asthma	2	
Healed tuberculosis	2	
Chronic bronchitis	2	15
Pulmonary fibrosis, marked	1	
Cystic disease of lung	1	
Bronchogenic carcinoma	1	
Metastatic carcinoma (from teratoma of testis)	1	
Total	71	

Symptoms: Pain, dyspnea, cough and weakness were the symptoms most frequently noted. Ninety per cent complained of pain or dyspnea—79 per cent had both pain and dyspnea. Pain, dyspnea, and cough were encountered as a triad in 24 per cent of the cases.

Previous Pneumothorax: Nineteen (28 per cent) of the patients in this review gave histories of 40 previous episodes of spontaneous pneumothorax. In only two of these patients was the pneumothorax on the contralateral side.

Relation to Activity: With respect to activity at onset, 25 were engaged in some form of active exertion, such as lifting, walking, coughing, or running. The others were at rest. Four awoke with pain and five noted onset of symptoms while getting out of bed. One complained of symptoms following an asthmatic attack.

Smoking: While a definite relationship between smoking and spontaneous pneumothorax has not been demonstrated, some authors feel that the chronic bronchitis and cough resulting from excessive smoking may aggravate focal emphysema. Of the 67 patients in this review, 67 per cent smoked between one-half and two packs of cigarettes per day, while only three were non-smokers.

Laboratory Findings

Pneumothorax was confirmed by x-ray film inspection in all except one (Table 2). Of the 67 patients, 25 had the tuberculin test, of whom eight reacted. The observations at thoracoplasty in 29 patients are recorded in Table 3.

TABLE 2—X-RAY FINDINGS

Side Involved	No.	Per cent
Right	42	61
Left	29	39
	71	
Degree of Pneumothorax		
Less than 20 per cent		9
20 - 50 per cent		20
More than 50 per cent		41
Clinical diagnosis		1
		71

Other X-ray Findings	
Effusion	23
Emphysema	5
Bullae or blebs	5
Adhesions	9
Density	4
Mediastinal shift	2
Calcifications	2
Pneumomediastinum	1
Diffuse severe fibrosis	1
Pleural plaque	1

TABLE 3—FINDINGS AT THORACOSCOPY

Negative	13)	
Blebs	9)	
	)	29
Adhesions	3)	
Leak	4)	
	29	

Treatment and Early Results

Methods of treatment are summarized in Table 4.

TABLE 4—METHOD OF TREATMENT

Method	Cases	Average for Expansion	Average Hospital Stay	Failures	Recurrences
Bed rest	17	17 days	22 days	2	4
Intercostal suction	39	2 days	12.5 days	4	4
Needle aspiration	7	7 days	12.5 days	3	1
Water seal	1	(Expired at 33 days of bronchogenic carcinoma)			
Chemical pleurisy	1	46 days	61 days		
Pneumoperitoneum	1	15 days	5 days		
Thoracotomy	5	days	42 days		
	71	days	days		

Bed rest: The initial treatment in 19 was bed rest in whom expansion failed to occur in two after 11 and 15 days and intercostal suction was, therefore, instituted. The remaining 17 were treated successfully with bed rest alone. Expansion required an average of 17 days and the average period of hospitalization was 22 days. The time for expansion was markedly influenced by the original degree of collapse as is shown in Table 5.

TABLE 5—DEGREE OF PNEUMOTHORAX AND PERIOD FOR EXPANSION

	Bed Rest		
Per cent Pneumothorax	Cases	Average for Expansion	Extremes
Less than 20	8	10.5 days	8-15 days
20 to 50	5	23 days	12-60 days
More than 50	4	24 days	17-33 days
	17		

Intercostal Catheter with Suction: There were 39 (55 per cent of this series) treated by this method,[5] according to a standardized technique as follows:

1. Pneumothorax is confirmed by x-ray films.
2. Thoracoscopy is performed under local anesthesia in the operating room through second anterior interspace in midclavicular line.
3. Through the thoracoscope sheath a No. 18 F Foley catheter (5 ml. bag) is inserted; the bag is inflated and withdrawn to the chest wall. The catheter is secured to the skin with a single stitch. If thoracoscopy is not performed, the catheter is inserted through a trocar.
4. Negative pressure (25 cm. water) is immediately applied to catheter and a chest x-ray film is obtained.

5. Suction (25 cm. of water) is continued for three days with patient at bed rest. X-ray film of chest is then repeated.
6. If lung is completely expanded, suction is discontinued and the catheter is placed on water-seal drainage for two days. At the end of this period, chest x-ray film is repeated. If the lung has remained expanded, the catheter is removed and the patient is discharged in one or two days. If pneumothorax has recurred, suction on the catheter is resumed and the above cycle repeated.
7. Resume normal activity after one week.

The average time for expansion by the above procedure was two days and the hospital stay averaged 12.5 days. In five patients, pneumothorax recurred during the period of water-seal drainage necessitating further suction. Intercostal suction was used only in those with a significant degree of pneumothorax.

Intercostal catheter suction failed to expand the lung in four patients. Thoracotomy was required because of persistent air leak from blebs in two of these patients. The remaining two failures of the method were in complicated cases; one had extensive pulmonary fibrosis and the other terato-carcinoma of the lung with chronic pneumothorax.

Needle Aspiration: In seven patients, most of whom had collapse of more than 20 per cent, the lung expanded after one or more needle aspirations. In three additional patients, needle aspiration failed and intercostal catheter suction resulted in prompt relief.

Thoracotomy: Five underwent thoracotomy. Two of these, as noted above, represent failures with intercostal catheter suction. Two others were operated upon when they entered with their third and fourth recurrences. The remaining patient underwent thoracotomy when progression of the pneumothorax occurred with rest, needle aspiration, and water seal.

Complications and Deaths

The only complications in this series were in two patients treated with intercostal catheter suction. Both of them developed pneumonitis on the involved side; however, in neither was the length of hospitalization increased. The systemic reaction to intercostal catheter suction was minimal in all other cases. Formerly, antibiotics were administered prophylactically to patients during suction treatment, but this proved unnecessary and is no longer our practice.

Eight patients in this series died during their period of hospitalization, (from a variety of conditions: carcinomatosis, cerebrovascular accidents, etc.). In none could the method of treatment used be considered a primary or contributing cause of death.

Recurrence

After discharge from the hospital there were five known recurrences in a group of 24 patients treated by bed rest and needle aspiration. In the group of 39 treated by intercostal suction there were four recurrences, Table 4. However, the follow-up information available is inadequate to permit valid conclusions regarding the relative merits of intercostal catheter suction in the prevention of recurrent pneumothorax.

In a definitive group of 29 patients following more than six months, there were four recurrences after bed rest or needle aspiration in nine and two recurrences after intercostal catheter suction in 20. Applying the appropriate statistical test (Chi square) which includes the correction factor for the small number of cases, the differential rates of recurrence between intercostal catheter suction and bed rest do not differ significantly from chance (P=.15).

Discussion

The aims of treatment in spontaneous pneumothorax are: (1) to alleviate symptoms, (2) to prevent complications, (3) to reduce morbidity and economic loss, and (4) to prevent recurrences. While there are several effective methods of therapy, obviously no one is suited to all cases. Since, as has been shown, a pneumothorax of less than 20 per cent will resolve on bed rest alone in eight to 15 days, treatment by bed rest alone should be used for all pneumothoraces of minor degree. If, however, expansion does not occur with bed rest, one must resort to other means to obtain expansion and to prevent the complications resulting from chronic pneumothorax.

Intercostal catheter suction is a safe and effective means of treating spontaneous pneumothorax. Symptoms are promptly relieved, complications are avoided, and morbidity is less than with other forms of therapy. For spontaneous pneumothorax exceeding 20 per cent, or where expansion does not occur with more conservative measures, intercostal catheter suction is the treatment of choice. During the past year, several patients have been treated successfully by applying suction to a small plastic catheter introduced into the pleural space through a No. 13 needle. However, with a large, persisting pleural leak it may be necessary to introduce a catheter in the manner outlined to produce complete expansion.

Some authors[3] feel that thoracoscopy is a time consuming and unrewarding procedure. Yet, as was noted in this review, positive findings were reported in 16 of the 29 cases in which it was done (Table 3). If blebs were visualized on thoracoscopy, this might be a factor in determining the form of treatment to be used if the patient should develop recurrent pneumothorax. Done at the time of insertion of the intercostal catheter, thoracoscopy is a simple procedure adding but a few minutes to the entire operation.

SUMMARY

1. Seventy-one instances of spontaneous pneumothorax have been reviewed, not all of which were the simple or idiopathic type.

2. Nineteen (28 per cent) had prior pneumothorax.

3. Of 19 treated with bed rest alone, there were two failures and four known recurrences. The average hospital stay was 22 days.

4. Of 39 treated with intercostal catheter suction, the average hospital stay was 12.5 days. There were four failures and four recurrences.

5. There was no significant complication associated with treatment by intercostal catheter suction.

6. Thoracoscopy was done in 29 and positive findings were recorded in 16. We believe thoracoscopy in addition to x-ray an important aid in determining whether to recommend open thoracotomy or an initial trial with catheter suction.

7. With an initial spontaneous pneumothorax of less than 20 per cent, in the absence of demonstrable large peripheral blebs, bed rest may be the treatment of choice. When it exceeds 20 per cent and initial open thoracotomy does not seem justifiable, intercostal catheter suction therapy, as described, has proven to be a safe and effective method of treatment in a high percentage of our cases.

RESUMEN

1. Setenta y un casos de neumotorax espontaneo se revisan. No todos ellos fueron del tipo simple idiopático.

2. Diecinueve (20 por ciento) habían tenido antes neumotorax.

3. De los 19 tratados con solo reposo en cama hubo dos fracasos y cuatro recurrencias conocidas. El tiempo medio de permanencia en el hospital fue de 22 días.

4. De 30 tratados con cateter intercostal y succión, el tiempo de permanencia en el hospital fue de 12 días. Hubo cuatro fracasos y cuatro recurrencias.

5. No hubo complicación de importancia despues del tratamiento con cateter.

6. La toracoscopía se hizo en 20 y hubo hallazgos positivos en 16.

7. Con neumotorax de menos de 20 por ciento el reposo en cama es el tratamiento de elección. Cuando es mayor de 20 por ciento o bien si otros métodos fallan el tratamiento con el catcter y aspiración es seguro y efectivo.

RESUMÉ

1. L'auteur passe en revue 71 cas de pneumothorax spontané. Certains d'entre eux n'étaient pas du type simple ou idiopathique.

2. 19 cas (28%) avient eu antérieurement un pneumothorax.

3. Sur les 19 traités par le repos au lit seul, il y eut deux échecs et quatre rechutes. Le séjour moyen à l'Hôpital fut de 22 jours.

4. Sur 30 cas traités pra aspiration à l'aide d'une sonde interpleurale, le séjour moyen à l'Hôpital fut de 12.5 jours. Il y eut quatre échecs et quatre rechutes.

5. Il n'y eut pas de complication nettement en rapport avec le traitement par aspiration.

6. Une thoracotomie fut faite dans 20 cas et des constatations positives furent enregistrées dans 16 cas.

7. Avec un pneumothorax qui entraine une diminution respiratoire de moins de 20%, le repos au lit est le traitement de choix. Lorsque la diminution dépasse 20% ou lorsque les autres méthodes de traitement échouent, l'aspiration par sonde est une méthode de traitement sans danger et efficace.

ZUSAMMENFASSUNG

1. Von den bei 71 Patienten beobachteten spontanen Pnth. entsprachen nicht alle dem einfachen oder idiopathischen Typ.

2. 19 (28%) hatten bereits früher einen Pnth.

3. Die lediglich verordnete Bettruhe bei 19 Patienten hatte in 2 Fällen keinen Erfolg, bei 4 Patienten kam es später zu einem erneuten Pnth. Der durchschnittliche Krankenhausaufenthalt dauerte 22 Tage.

4. Bei 30 Patienten, bei denen die Luft durch Intercostalkatheter abgesaugt wurde, betrugt die durchschnittliche stationäre Behandlung 12.5 Tage. Dabei erwies sich die Therapie bei 4 Patienten als Misserfolg. In 4 Fällen trat später erneut Pnth. auf.

5. Durch die Behandlung mit Intercostalkatheter wurden keine besonderen Komplikationen verursacht.

6. In 20 Fällen wurde eine Thorakoskopie durchgeführt, durch die bei 16 Patienten ein Befund erhoben werden konnte.

7. Bei einem Pneumothorax von weninger als 20% ist Bettruhe die Methode der Wahl. Wenn er 20% übersteigt oder andere Behandlungsmethoden versagen, stellt das Absaugen der Luft durch Intercostalkatheter eine sichere und wirkungsvolle Methode dar.

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Effect of Direct Irradiation on the Course of Pulmonary Tuberculosis (Using Cancerocidal Doses)*,**

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The primary objective of this study was to determine whether there is any hazard in the use of irradiation to the thorax for neoplastic disease coexistent with pulmonary tuberculosis.

The association of lung cancer and pulmonary tuberculosis has become a problem of much significance. There has been in recent years a striking increase in lung cancer incidence and mortality. Tuberculosis which heretofore had been a disease chiefly of young adults has become a disease of middle age and older persons, predominantly men. Longevity has increased in tuberculosis patients. Lung cancer and pulmonary tuberculosis are therefore prevalent in the same age and sex group, namely, the older man. The expectation is that the frequency of this coexistence will continue to increase. In the predrug era, there were few reports of carcinoma associated with tuberculosis, as many tuberculosis patients died before reaching the cancer age. In recent years, there have been a good number of reports of coexistent pulmonary tuberculosis and primary lung cancer.[1-13] In these, when therapy is discussed, the possibility of surgery for the neoplasm is considered. X-ray therapy for inoperable or unresectable carcinoma in the presence of tuberculosis is not recommended apparently because of the accepted opinion that irradiation of a tuberculous lesion will cause its reactivation. On theoretic consideration, it was our belief that pulmonary tuberculosis under effective control of antituberculosis drugs would not contraindicate the application of radiotherapy. A preliminary study of the effect of irradiation in eight patients with pulmonary tuberculosis under the cover of antimicrobial therapy was carried out in the New York City Municipal Sanatorium at Otisville, New York in 1953 and 1954. This study was stimulated primarily by Dr. Fred Elias, the roentgenologist. In this experience, it was found that with antituberculosis drugs being used, radiotherapy with small and moderate doses (400 r to 2000 r [air] and the mid-lung dose with the factors used averaged 30 per cent of the air dose) could be administered directly to active pulmonary tuberculosis of cavitary nature without danger of deterioration of the tuberculosis. It was, therefore, planned to carry this work a step further and we felt justified in using larger x-ray doses where indicated. In the present study, cases of inoperable lung cancer

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coexistent with pulmonary tuberculosis were irradiated for palliation or possible cure. These patients were irradiated during the period from December, 1956 to November, 1958. These radiation doses were much higher than those previously reported. All of the patients were on antituberculosis drug treatment. It was believed that this would permit the essential radiation treatment to be administered. There were seven patients in this group (all treated in the Bronx Municipal Hospital Center*) and the main findings follow.

Case 1: A. B., a 70 year-old white man was admitted on October 23, 1956 with extensive soft and cavitary tuberculosis in the upper and apex of the lower lobe of the right lung (Fig. 1). Under antituberculosis drug therapy (SM, PAS, and INH)** sputum conversion occurred within two months. A dense lesion then appeared in the right upper lobe with retraction of the mediastinum. Bronchoscopic biopsy of a granular lesion at the right upper lobe orifice revealed squamous carcinoma. There was excellent resolution of the tuberculous areas so that in nine months there was only residual fibrosis. The neoplasm developed steadily in the right upper lobe. The sputum was negative for ten months and the antituberculosis drug treatment had been in use for 12 months before radiation therapy was given, prompted by the appearance of a superior vena caval syndrome (Fig. 2). With Cobalt-60 teletherapy to 10 x 15 cm. right upper lobe portals, a tumor dose of 4000 r was given in 32 treatments over a period of three and one-half months (October 2, 1957 to January 14, 1958). At the end of irradiation, there was no roentgenographic change. The patient survived for 14 months and one week after completion of radiation therapy. During this period, many sputum cultures were negative except for a single positive culture three and one-half months before death (almost 11 months after irradiation) and two years after the last previously positive culture. The chest x-ray films were unchanged for ten months after completion of irradiation and then revealed an increase in the diffuse density in the right upper lobe and greater deviation of the trachea and mediastinum. The roentgenograms remained unchanged during the next four months prior to death. He died on March 21, 1959 after several hemoptyses. On necropsy, at the carina and mouth of the right upper lobe bronchus was an ulcerating fungating friable mass.

*Some of these cases were treated under the supervision of Dr. Charles Botstein.

**SM refers to streptomycin, PAS refers to para-aminosalicylic acid, and INH refers to isoniazid.

FIGURE 1

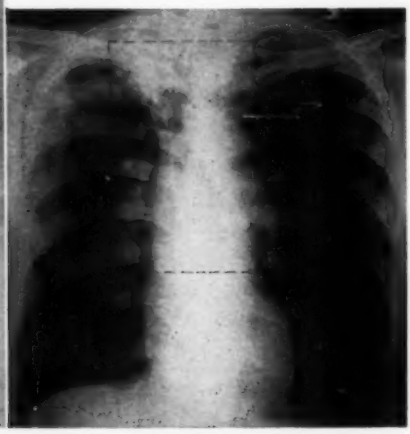

FIGURE 2

FIGURE 1 (Case 1): Admission film. Extensive tuberculosis right lung with coalescent exudative-productive lesions and subapical cavitations. FIGURE 2 (Case 1): Prior to irradiation (irradiated area outlined). Excellent resolution of tuberculosis. Dense neoplastic lesion in medial part right upper lobe. Slight retraction of trachea, mediastinum.

The remaining lung parenchyma showed marked anthracosis and honeycombed appearance. Sections through the right upper lobe showed a squamous cell carcinoma arising in the bronchial mucosa with invasion of the surrounding lung parenchyma. There was marked chronic inflammatory cell infiltration of the bronchus and marked fibrosis and chronic inflammatory cell infiltration in the areas of tumor invasion and some necrosis of the tumor. Most of the adjacent tissue showed fibrosis and increased vascularity. Scattered foci of collapsed lung parenchyma were noted and many thick-walled blood vessels, some of which had organized thrombi. These changes were interpreted as radiation effect. Beneath the wall were localized masses of hyaline, resembling old healed tuberculosis.

Comment: This patient, with extensive tuberculosis in the right lung, having had 29 months of antituberculosis drug treatment, controlled his tuberculosis and reached an arrested state. The 4000 r given for the carcinoma which developed in the right upper lobe did not, in the 14 months the patient lived after the radiation treatment, cause any exacerbation of the tuberculosis. The chest x-ray film changes in the terminal period were due to the advancing neoplasm. The single positive culture noted three and one-half months before death is apparently not indicative of an unstable, active or relapsing tuberculosis. Rather it can be explained as probably due to an incidental release of a few bacilli from the carcinoma invading an old controlled focus of tuberculosis. The necropsy findings would confirm this as the tuberculosis appeared old, and fibrotic with no active lesion.

Case 2: R. W., a 43 year-old colored man, was admitted June 6, 1956. Chest x-ray film showed extensive soft nodular and conglomerate infiltrations in both lung fields and right pleural effusion. Sputa were positive for acid-fast bacilli and antituberculosis drugs (SM, INH and PAS) were started. There was marked clinical improvement and steady resolution of the pulmonary infiltrations, leaving coalescent nodular apical residuals. The sputum cultures became negative within two months and remained so except for one culture seven months after admission. He was discharged on March 12, 1957, but was re-admitted 13 months later (April 24, 1958) with unchanged apical infiltration, but with a new left hilar mass and infiltration extending into the lingula of the left upper lobe. Left thoracotomy revealed tuberculosis in the left upper lobe and a hard mass at the hilum which, on biopsy, showed a metastatic nonkeratinizing epidermoid carcinoma. Radiation therapy was started five months after readmission with Cobalt-60 teletherapy to the left upper chest through anterior and posterior ports of 10 x 14 cm. with a total tumor dose of 4300 r in 49 days (October 2, 1958 to November 9, 1958). This irradiation was given over an area of tuberculosis. After radiation therapy, the apical tuberculous areas remained unchanged and the left hilar and parahilar involvement decreased in size. He was discharged March 11, 1959, four months after irradiation. The sputum and gastric cultures had remained negative. A month and a half after discharge, the left hilar and para-hilar involvement was considerably increased, but the tuberculous areas were unchanged. He died June 7, 1959, seven months after irradiation with a final diagnosis of epidermoid carcinoma of the lung with metastases to the pleura.

Comment: In this case, extensive bilateral pulmonary tuberculosis improved considerably with antituberculosis drugs. Carcinoma developed in the left hilum and lingula. Irradiation was given to the left upper lobe and mediastinum. The patient had been under antituberculosis drug therapy for 28 months and was last positive for tuberculosis 21 months before irradiation was started. During irradiation the residual nodular apical tuberculous infiltration did not change. In a follow-up period of seven months after completion of irradiation, there was temporary regression of the tumor and then a considerable increase with the neoplasm causing death. The tuberculosis roentgenologically showed no change and the sputum and gastric cultures remained negative. The tuberculosis was well controlled by drug treatment. The 4300 r given for the tumor in the left upper lobe did not in the seven months he lived after radiation treatment cause any exacerbation of the tuberculosis.

Case 3: B. B., a 44 year-old colored man, was admitted on September 13, 1957, with extensive bilateral upper lobe tuberculosis with nodular mottling and a 2 cm. cavity in the right subapical area. On antituberculosis medication (INH and PAS) there was considerable improvement with residual fibro-nodular areas in the upper lobes, but persistence of the right subapical cavity. The sputum remained frequently positive for acid-fast bacilli. Within eight and one-half months a left parahilar density developed. This increased in size and was associated with pain in the dorsal spine, a paraspinal mass and destructive changes in D5 and D6. Biopsy of the mass revealed adenocarcinoma. Streptomycin was added to the drug regimen. The sputum cultures continued to be positive for acid-fast bacilli until two months before irradiation. The nodular upper lobe infiltration appeared smaller and more fibrotic with the right subapical cavitation persistent. Radiation treatment was started one year after admission (and 14 months after initiation of antituberculosis drug therapy) with Cobalt-60 teletherapy to the left chest over the tumor mass. Over a 67-day period (September 1, 1958 to November 6, 1958) a total tumor dose of 5300 r to the spine and 5100 r to the left mid chest was delivered through anterior and posterior ports of 14 x 17 cm. He lived seven weeks after completion of irradiation with death on December 28, 1958. The sputum culture was positive for acid-fast bacilli within five

weeks of the beginning of irradiation and then remained negative until death—a period of two months and 19 days. The chest films after irradiation revealed a slight decrease in the parahilar density, but no change in the bilateral upper lobe tuberculosis. The necropsy revealed primarily adenocarcinoma in the left upper lobe and apex of left lower lobe with extensive regional and distant metastases and secondarily inactive pulmonary tuberculosis with pulmonary emphysema and fibrosis. Microscopic sections revealed infiltrating, poorly differentiated adenocarcinoma with many areas of necrosis and hemorrhage within the tumor. Sections of lung showed diffuse fibrosis and focal emphysema. In the upper lobe were several caseating granulomata with thick fibrous capsules. Adjacent tissue showed marked fibrosis but typical features of radiation changes were lacking. The diagnosis was that of healed encapsulated fibrocaseous tuberculosis.

Comment: In this case with extensive bilateral upper lobe tuberculosis there was much improvement with antituberculosis drugs. An adenocarcinoma developed in the left lung and irradiation was given through the tuberculosis in the left upper lobe. The sputa were positive until two months before irradiation was started. A single sputum was positive five weeks after irradiation was started and then all sputa were negative until death occurred two and one-half months later. Necropsy revealed fibrosis and well encapsulated fibrocaseous foci and no active tuberculosis. The evidence indicates that with the antimicrobial coverage the 5100 r to the lung did not cause any exacerbation of the tuberculosis and the healing was maintained.

Case 4: R. S., a 56 year-old white man, was admitted on November 23, 1956. He was known to have pulmonary tuberculosis at least four and one-half years before a definite diagnosis of right upper lobe epidermoid carcinoma was made by bronchoscopic biopsy. He had been under antituberculosis drug treatment (SM, INH and PAS). There was fibrocalcific nodular infiltration in the upper halves of both lungs with coalescent soft infiltration and cavitation in the left upper lobe. The carcinoma appeared as a mass in the right paratracheal area, extending toward the apex (Fig. 3). Radiation therapy was started within one month after admission. The sputum had been positive prior to irradiation. Radiotherapy was given with grid technique (250 Kv) to the right upper anterior and posterior chest through 10 x 15 cm. ports with a total tumor dose of 5100 r in 51 days (December 20, 1956 to February 8, 1957). One month after irradiation there was much reduction in the right paratracheal mass, but the cavitary area in the left upper lobe increased. There was no irradiation to the left lung and it is probable that this change was due to the chronic relapsing character of the tuberculous disease in a patient uncontrolled after years of antimicrobial treatment. The sputum continued to be positive for acid-fast bacilli. Ten months after radiation therapy, the cavity in the left upper lobe decreased in size. *In vitro* resistance to INH and PAS was present. Antituberculosis drug treatment was continued, but the sputum remained positive. Another antituberculosis drug (cycloserine) was added. Sixteen months after irradiation, the right paratracheal mass began to enlarge again. By this time, there had been much clearing of the lesion in the left upper lobe (Fig. 4). By April, 1959, 26 months after completion of irradiation, there was complete atelectasis of the right lung. The left lung appeared emphysematous with no change in the

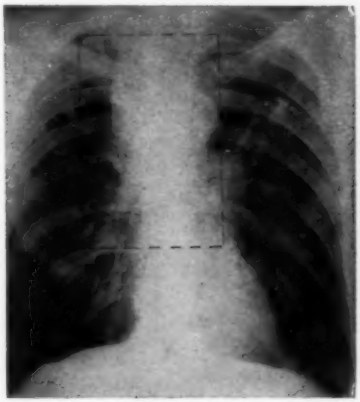

FIGURE 3

FIGURE 4

FIGURE 3 (Case 4): Admission film. Tuberculous fibrocalcific nodular lesions in upper lung fields with coalescent soft infiltration and cavitation in left upper lobe. Malignant mass in right paratracheal area. (Irradiated area outlined.) FIGURE 4 (Case 4): Sixteen months after irradiation. Right paratracheal mass enlarging. Pleural effusion right. Much clearing of left upper lobe lesion.

infiltration, but the suggestive cavity in the left upper lobe was smaller than before irradiation. The sputa were often positive. The clinical condition deteriorated and he died from the carcinoma on October 29, 1959 or thirty-two and one-half months after irradiation.

Comment: There was extensive fibrocalcific tuberculous involvement in the upper lobe of the right lung (and fibrocalcific and soft infiltration and cavitation in the upper lobe of the left lung). Fifty-one hundred r was given to the right upper lobe where a carcinoma had developed. He survived for thirty-two and one-half months after irradiation. For six months before death, the tuberculosis in the right upper lobe could not be visualized because of complete right lung atelectasis due to the tumor. During the long period before this atelectasis, there was no roentgenologic change in the tuberculosis in the right upper lung. He had tuberculosis at least four and one-half years before cancer was diagnosed. The sputa remained positive throughout the course of treatment due to a persistent cavitary lesion in the left upper lobe and bacterial resistance to antituberculosis drugs. At death, the left lung had shown much resolution and the cavity was smaller compared to the status prior to irradiation. Although an autopsy was not done, there was no clinical indication of deterioration of the tuberculosis due to irradiation.

Case 5: W. M., a 61 year-old white man, was admitted May 21, 1957 after 26 months' hospitalization elsewhere. His first x-ray film had revealed extensive bilateral pulmonary tuberculosis with confluent soft areas and cavities in the upper lobes and soft linear nodular infiltration in the rest of the lungs. The sputum was positive for acid-fast bacilli and remained so for 11 months. He was placed on antituberculosis drug treatment (SM and INH) with marked resolution. After one year, the lower lung fields were clear, but there was residual linear and nodular fibrosis in the apical and subapical areas. However, a mass appeared in the right parahilar area nine months after the first admission and increased slowly. The sputa and cultures remained negative. On admission to Bronx Municipal Hospital Center, sputum examinations were positive for malignant squamous cells and needle aspiration of the right lung mass revealed malignant cells. Radiation therapy was started two and one-half months after admission. At this time there was a homogeneous density of the right upper lobe. Cobalt-60 irradiation was given to the right upper lung through anterior and posterior portals 14 x 14 cm. for a period of 37 days (August 7, 1957 to September 12, 1957) with a tumor dose of 5200 r. After completion of therapy there was a slight decrease in the mass with more right upper lobe retraction. The tuberculous infiltrations in the right upper lobe could not be visualized and the left lung was unchanged. Clinical deterioration continued. Terminally he developed right hemiplegia from metastasis to the brain, became comatose and died on December 24, 1957, three and one-half months after completion of irradiation. There were no roentgenologic changes during this period. The sputum had remained negative for tuberculosis.

Comment: In this patient, extensive bilateral soft and cavitary pulmonary tuberculosis had undergone marked resolution with antituberculosis drugs leaving only residual fibrosis in the upper lobes. The sputum which had been persistently positive for tuberculosis became negative 11 months after start of drug therapy and remained so the rest of his life. Fifty-two hundred r was given for a right upper lobe neoplasm and through an area of tuberculosis. He died three and one-half months after irridiation. There was no change in the tuberculosis in the left lung and visible lung field on the right. This case is more difficult to evaluate because the follow-up period was short and there was no necropsy. However, the tuberculosis in the visible lung field appeared well controlled by antimicrobial therapy following irradiation.

Case 6: T. H., a 51 year-old white man, was admitted January 4, 1957. He had diffuse infiltration throughout the right lung, with linear infiltration and mottling throughout the right upper lobe with suggestive small radiolucent areas. He was on antituberculosis drugs (SM and PAS). Within two and one-half months after admission, bronchoscopy revealed a neoplasm in the right main bronchus with tissue section showing an infiltrating squamous cell carcinoma. The chest film had shown enlargement of the right hilum. The tuberculosis responded to antituberculosis drug therapy, the sputa and gastric washings were negative for acid-fast bacilli, and just prior to irradiation there had been moderate resolution of the linear and nodular infiltration in the right lung. The right parahilar density was larger and there was retraction of the upper lobe. Irradiation was started four and one-half months after admission with Cobalt-60 to the right upper lung field through anterior and posterior portals 14 x 16 cm., with a total tumor dose of 5400 r in 75 days (April 18, 1957 to July 1, 1957). The irradiation was given through an area where the major roentgenologic evidence of tuberculosis had been present. The film at completion of irradiation showed more atelectasis of the right lung and encapsulated right pneumothorax. The roentgenologic changes in the tuberculosis could not be determined and the left lung remained clear. There was a follow-up period of five months after radiation therapy. The irradiation was associated with some temporary symptomatic improvement. The sputum and gastric cultures continued to be negative. He died on December 7, 1957, five months and one week after completion of therapy with terminal kidney failure. Necropsy revealed the right upper main bronchus markedly narrowed by neoplastic tissue which extended into the lung parenchyma. The right lung was quite rigid and

showed a diffuse mesh-like pattern of neoplastic infiltration throughout forming irregular circumscribed nodular honeycombed areas. The lung on section showed not only the keratinizing squamous cell carcinoma but areas of edema and fibrosis. In addition there were scattered fibrocaseous nodules with occasional Langhans' type giant cells. No definite change attributable to radiation was recognized.

Comment: The patient had extensive tuberculosis in the right lung, especially the upper half, with moderate resolution under antituberculosis drugs and sputum conversion. A neoplasm developed in the right lung and he received 5400 r to the right upper lung field where tuberculosis had been present. He survived five months after completion of irradiation. The sputa continued negative, the left lung remained clear and there was no roentgenologic evidence of spread of tuberculosis, although the atelectasis obscured details in the right upper lobe. At necropsy the tuberculous foci appeared old and fibrocaseous. There was no evidence of exacerbation of the tuberculosis.

Case 7: C. K., a 68 year-old white man, was transferred on May 22, 1957. In the first institution, to which he had been admitted in October, 1956, it was noted that he had tuberculosis in the right upper lobe with small cavities. A coexistent homogeneous right upper lobe density (Fig. 5) was proved due to epidermoid carcinoma of the bronchus by bronchoscopic and scalene node biopsies. The tuberculosis was confirmed by three positive sputum cultures. With antituberculosis drug therapy (SM and INH) sputum conversion occurred. The right upper lobe neoplasm progressed to create a uniform lobar density. Irradiation was given (250 Kv) with a total tumor dose of 2000 r in 30 days (March 18, 1957 to April 17, 1957), less than six weeks after antituber-

FIGURE 5

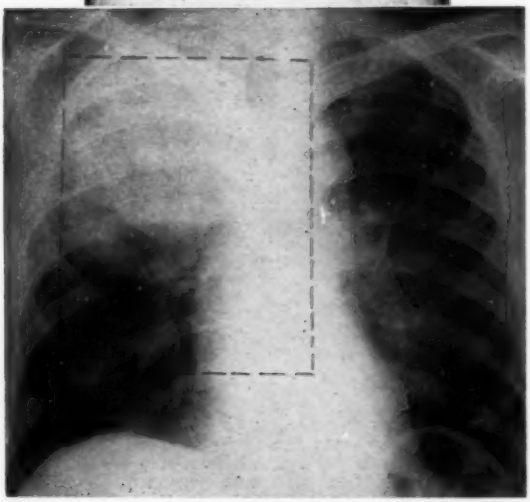

FIGURE 6

FIGURE 5 (Case 7): Film at onset. Tuberculous infiltrations in right upper lobe and subapical cavities. Homogeneous neoplastic density at base of right upper lobe.
FIGURE 6 (Case 7): After first course of irradiation. Extensive homogeneous density right upper lung field. (Area irradiated during second course of irradiation outlined.)

culosis drugs were started and only a few weeks after sputum conversion. On admission to the Bronx Municipal Hospital Center, the chest film showed an extensive homogeneous density in the right upper lung field (Fig. 6). INH and SM were continued. Two months after completion of the first course of irradiation, another course of irradiation with Cobalt-60 teletherapy was given. A total tumor dose of 6800 r was given in 52 days (June 20, 1957 to August 9, 1957) to the right upper chest, through anterior and posterior portals of 12 x 15 cm. He had a total tumor dose of 8800 r in five months to the right upper lung field, the area of the pulmonary tuberculosis. After irradiation there was subjective improvement with much reaeration of the right upper lobe (Fig. 7). Sputum smears and cultures prior to irradiation were negative, but there was no sputum report available during or immediately after irradiation. He was discharged to clinic supervision on August 30, 1957, three weeks after completion of irradiation. He never returned to the out patient department. There is a serious question as to whether he continued his antituberculosis drug therapy after discharge. He was re-admitted to another hospital on November 1, 1957, two months after discharge. Based on previous hospitalization for tuberculosis, antituberculosis drugs were started one month after readmission. A sputum smear on November 7, 1957, two months before death, was negative, but the culture was positive for acid-fast bacilli. The last chest x-ray film, two months before death, revealed considerable change, with destruction of the right upper lobe and bilateral diffuse infiltration (Fig. 8). He died on January 9, 1958, five months after irradiation. The cause of death clinically was carcinoma of the lung with inactive, moderately-advanced chronic pulmonary tuberculosis.

Comment: This patient had tuberculosis in the upper lobe of the right lung and carcinoma developed in the same area. Sputum conversion occurred rapidly with antituberculosis drugs. He survived five months after completion of irradiation with 8800 r given to the right upper lung field. Because of atelectasis in the right upper lobe the roentgenologic changes in tuberculosis could not be discerned, but there was much

FIGURE 7

FIGURE 8

FIGURE 7 (Case 7): At completion of second course of irradiation. Much reaeration of right upper lobe. FIGURE 8 (Case 7): Three months after second course of irradiation. Destruction of right upper lobe. Diffuse infiltration in rest of right lung and left lung.

reaeration of the lobe after irradiation. A film two months before death showed destruction of the right upper lobe with bilateral diffuse pulmonary infiltration. A sputum culture at this time was positive for acid-fast bacilli. The crucial question is whether there was progression of the tuberculosis. It is not certain whether the final chest x-ray film shows necrosis of tumor with progression of malignancy and lymphangitic spread or relapsing tuberculosis. There are several possibilities for the positive culture: (a) was this a true tuberculosis relapse due to discontinuation of the antituberculosis drugs for three months after irradiation?; (b) did the unusually heavy dose of irradiation (8800 r) cause lung necrosis?; (c) did the neoplasm extend into healing areas of tuberculosis and release a few acid-fast bacilli without a true relapse of the tuberculosis? In any case, positive bacteriologic findings are evidence of relapsing tuberculosis by our criteria and a positive culture was found two months before death and three months after irradiation. The issues considered above prevent a definite conclusion that this was due to the radiation therapy although this cannot be excluded. It must be emphasized that the continuation of anituberculosis drugs is a basic requirement to avoid the possibility of any worsening of the tuberculosis from irradiation.

Discussion

The seven patients in this series with lung cancer and pulmonary tuberculosis given radiation therapy were men, aged 43 to 70. The known duration of the tuberculosis varied from four months to four and one-half years. The tuberculosis prior to irradiation appeared in one patient as fibrocalcific nodulation, in another as dense infiltration and small cavities, and five had soft mottled infiltrations with cavities. Before irradiation, various degrees of resolution and healing had occurred, leaving residual coalescent or fibrotic linear and nodular lesions. It may be significant that there was no recent large caseous pneumonic area or acute cavity.

At the start of irradiation, the sputu mwas still positive in two and negative in five patients. In these latter five cases the sputum had been negative for intervals of two to 21 months. The tuberculosis was active in two, arrested in three and inactive in two.

Antituberculosis drugs had been given in each case for varied periods prior to irradiation—from one month to four and one-half years. These drugs were continued in every patient during the treatment period and in all but one after completion of treatment.

The primary lung cancer was present in the right upper lobe in five patients and in the left upper lung field in two. A histologic diagnosis was made in all patients, epidermoid carcinoma in six and adenocarcinoma in one.

The radiation therapy was given with Cobalt-60 in five, with 250 Kv grid technique in another and one had a first course elsewhere with 250 Kv followed by a second course with Cobalt-60. The mid-lung depth dose varied from 4000 r to 5400 r, and in the patient with two courses, 2000 r was given in the first and 6800 r in the second course. The irradiation was administered to anterior and posterior fields of 150 to 200 square cm. with daily treatments except when interrupted because of the patient's condition. Total treatment varied from 37 to 104 days (but most within two months).

The neoplasm in all seven patients developed in an area of lung where tuberculous lesions were present. Consequently, the stated tumor dose was given to areas of tuberculosis.

The duration of the follow-up after completion of irradiation, with all cases observed until death, varied from seven weeks to thirty-two and one-half months.

The possible changes in the tuberculosis that could be related to the radiation therapy were reviewed from the clinical, bacteriologic and roentgenologic aspects. Such changes were divided into three periods: first, during the actual time of radiation treatment; second, the six months immediately following irradiation (or until death if it occurred within six months of the radiotherapy) and third, the remaining period of observation.

During the treatment interval, there was no clinical finding of tuberculosis relapse or roentgenologic worsening in any case. One patient (Case 3) had a positive sputum culture five weeks after start of treatment and was then negative until death two and one-half months later. After irradiation, there was no change in the upper lobe tuberculosis. At necropsy, the lung revealed diffuse fibrosis with several caseous granulomata with thick fibrous capsules. There was no exacerbation of disease.

In the six-month period following completion of irradiation, there were three other patients, with death in one at three and one-half months (Case 5), and in two at five months (Case 6, Case 7). Clinically, there was general deterioration from progressive carcinoma in all three. In Case 5, the sputum remained negative and the tuberculosis in the visible lung field appeared well controlled after irradiation. The sputa continued negative in Case 6 and there was no roentgenologic evidence of spread of tuberculosis, although atelectasis obscured details. At necropsy, the tuberculous foci appeared old and fibrocaseous with no evidence of exacerbation. The sputum was positive in only one (Case 7). In this case, a positive culture was reported three months after completion of irradiation (and two months before death). There were, at this time, roentgenographic changes of lung destruction and diffuse bilateral infiltration. There is a possibility of progression of tuberculosis, but the changes could be due to the

unusually heavy dose of irradiation (8800 r) and radiation necrosis. An additional factor was that the antituberculosis drugs had been discontinued. The final opinion is, therefore, equivocal.

In evaluating the changes in tuberculosis over six months after irradiation, there are three patients to be considered. The clinical changes in these cases were terminal manifestations of carcinoma and death occurred at intervals of seven months (Case 2), 14 months (Case 1), and thirty-two and one-half months (Case 4). In Case 2, the sputum remained negative and the tuberculosis roentgenographically showed no change. A single positive culture was reported three and one-half months before death (11 months after irradiation) in Case 1. There had been no x-ray film change in the tuberculosis. At necropsy, the tuberculosis appeared old, fibrotic and healed, with no active lesion. In Case 4, there had been no roentgenologic change in the tuberculosis in the irradiated right upper lung for over 26 months after irradiation when terminal atelectasis from cancer developed. The sputa had been positive throughout treatment due to a persistent tuberculous cavitary lesion in the non-irradiated left upper lobe and bacterial resistance to antituberculosis drugs.

At the final observation of the patients the tuberculosis was considered inactive or arrested in all but two cases. Of the latter, one was definitely active (Case 4 with contralateral tuberculous cavitation), one was of questionable arrest (Case 7 with roentgenologic change and one positive culture and questionable relapse of tuberculosis).

SUMMARY

1. In this study, cases of inoperable lung cancer coexistent with pulmonary tuberculosis were irradiated with cancerocidal doses.

2. Seven patients in whom neoplasm developed in an area of tuberculosis were treated. The dose of irradiation at the central lung varied from 4000 r to 6800 r given in 37 to 104 days.

3. All patients received antituberculosis drugs.

4. The total period of observation after irradiation varied from seven weeks to thirty-two and one-half months.

5. In only one of the seven patients was there x-ray film evidence of change that could possibly be due to relapse of tuberculosis. In this patient (Case 7) the changes might be due to radiation necrosis (8800 r). This patient, moreover, had discontinued antituberculosis drug treatment after irradiation.

6. The experience in this small series of patients would indicate that irradiation of pulmonary neoplasms coexistent with pulmonary tuberculosis with cancerocidal doses can be accomplished without danger of deterioration of the tuberculosis if proper antituberculosis drug coverage is provided. In the presence of considerable drug resistance it would be desirable to add another antituberculosis drug to which the microorganism is sensitive to avoid any possible hazard of irradiation.

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RESUMEN

1. Este estudio presenta los resultados de casos de cancer pulmonar inoperable con tuberculosis pulmonar coexistente que se irradiaron con dosis cancericidas.

2. Se trataron siete enfermos en los que el cancer se desarrolló en el area en que la tuberculosis se trataba. La dosis de irradiación al centro pulmonar varió de 4,000 r a 6,800 r dada de 37 a 104 días.

3. Todos los enfermos recibieron drogas antituberculosas.

4. El período de observación total después de irradiación varió de 7 semanas a 32½ meses.

5. Solo en uno de los siete enfermos había evidencia radiológica de cambio que pudiese atribuirse a recaída de tuberculosis. En este enfermo (caso 7), los cambios podrían deberse a necrosis de radiación (8,000 r). Este enfermo además, había interrumpido el uso de la droga antituberculosa después de la radiación.

6. La experiencia con esta pequeña serie indicaría que la radiación en neoplasmas coexistentes con tuberculosis, con dosis cancericidas, puede realizarse sin peligro de deterioro en la tuberculosis si se protegen los enfermos con las drogas antituberculosas. En presencia de considerable drogorresistencia sería deseable agregar otra droga antituberculosa a la que la enfermedad sea sensible a fin de evitar cualquier complicación a la radiación.

RESUMÉ

1. Dans cette étude, des cas de cancer inopérable coexistant avec une tuberculose pulmonaire furent irradiés avec des doses destructives pour le cancer.

2. Sept malades chez lesquels une néoplasie se développa dans une zone de tuberculose furent traités. La dose d'irradiation à la partie centrale du poumon varia de 4,000 r à 6,800 r donnés en 37 à 104 jours.

3. Tous les malades reçurent des produits antituberculeux.

4. La période totale d'observation après irradiation s'étendit de 7 semaines à 32 mois et demi.

5. Chez un seul des 7 malades, il y eut des manifestations radiologiques qui pouvaient être imputables à une rechute de tuberculose. Chez ce malade (observation 7) les lésions pouvaient être dues à une nécrose radiothérapique (8,800 r) De plus ce malade avait cessé le traitement antituberculeux après l'irradiation.

6. Cette expérience faite sur un petit groupe de malades semblerait indiquer que l'irradiation des néoplasies pulmonaires coexistant avec une tuberculose pulmonaire peut être pratiquée avec des doses efficaces contre le cancer, sans danger de faire évoluer la tuberculose si un traitement antituberculeux bien fait est associé. En présence d'une résistance élevée au médicament, il est souhaitable d'ajouter un autre produit antituberculeux auquel le germe est sensible, pour éviter toute possibilité de danger imputable à l'irradiation.

ZUSAMMENFASSUNG

1. Bei dieser Untersuchung wurden Fälle von inoperablem Lungenkrebs, bei denen gleichzeitig eine Lungentuberkulose bestand, mit für Krebs wirksamen Dosen bestrahlt.

2. 7 Kranke, deren Neoplasmen sich im Bereich einer Tuberkulose entwickelt hatten, wurden auf diese Art behandelt. Die Strahlendosis im zentralen Lungengebiet schwankte zwischen 4000 r bis 6800 r, die in einer Zeitspanne zwischen 37 und 104 Tagen verabfolgt wurden.

3. Alle Kranken erhielten antituberkulöse Mittel.

4. Die gesamte Beobachtungszeit nach der Bestrahlung schwankte zwischen 7 Wochen und 32½ Monate.

5. Nur in einem Fall von 7 Fällen bestand auf der Thorax-Röntgenaufnahme ein Anhaltspunkt für Veränderungen, die möglicherweise einem Rückfall der Tuberkulöse zugeschrieben werden konnten. Bei diesem Patienten (Fall 7) waren die Veränderungen möglicherweise die Folgen der durch die Bestrahlung bewirkten Nekrose (8800 r). Dieser Kranke hatte aber außerdem nach der Bestrahlung mit der antituberkulösen Medikation aufgehört.

6. Die Erfahrung an dieser kleinen Reihe von Kranken würde doch darauf hinweisen, daß eine Bestrahlung von pulmonalen Neoplasmen, bei denen gleichzeitig eine Lungentuberkulose besteht, mit für Krebs wirksamen Dosen erfolgen kann, ohne Gefahr der Verschlechterun der Tuberkulose, sofern ein Schutz durch entsprechende antituberkulöse Medikamente gewährleistet ist. Bei Vorliegen einer erheblichen Resistenz wäre es wünschenswert, andere antituberkulöse Mittel hinzuzuziehen, auf die der Befund noch reagiert, um jede mögliche Gefährdung durch die Bestrahlung zu vermeiden.

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The Therapeutic Dividend of Roentgenographic Resurveys in a Psychiatric Hospital*

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Introduction

In a previous report,[1] it was pointed out that periodic roentgenographic resurveys of a captive population leads to a diminishing yield of new active cases of tuberculosis if an adequate control program is in effect. It is well known that surveys reveal tuberculosis of lesser extent more often than is the case when the discovery of the disease is dependent on the development of symptoms. Both of these factors tend to diminish the problem of tuberculosis. At the same time, it can be expected that therapeutic results will improve. The purpose of this paper is to document the fact that the results of therapy are excellent in a milieux of good tuberculosis control.

Method and Material

The Norristown State Hospital is a large psychiatric institution with approximately 4500 patients. In the admission wards, a 14 x 17 inch chest x-ray film is part of the routine examination. If the prognosis of the psychiatric illness is such as to warrant prolonged hospitalization and the prospects of cure are small, then the patient is transferred to one of the other buildings for resident care.

Since 1952, chest surveys by means of 70 mm. x-ray films have been done at two-year intervals among resident patients and at yearly intervals among employees. All patients whose film findings suggest active tuberculosis or advanced tuberculosis of undetermined activity (according to the 1955 National Tuberculosis Association Diagnostic Standards) were isolated for study and treatment as indicated. Those whose films suggested minimal tuberculosis, probably inactive, were simply followed with periodic films and isolated if roentgenographic change occurred. Since the spring of 1959, these cases have also been studied bacteriologically for three to six months, but this policy was established after the period to be considered in this report.

The third biannual survey was begun in June, 1956 and at that time, a careful follow-up system was instituted to be sure that all inactive cases of tuberculosis were rerayed at six to twelve month intervals on 14 x 17 inch films.

With this system of close roentgenographic control, there has been an impressive improvement in the type of active tuberculosis discovered in this institution and it has appeared that prognosis for "cure" of tuberculosis among resident patients has become exceedingly good. However, at the same time the tuberculosis wards have admitted patients with tuberculosis who were transferred from four other state psychiatric hospitals as the Norristown State Hospital became a psychiatric tuberculosis center. These referred cases have not fared as well as our own

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patients and a comparison will be made between those originating in our own hospital and the patients transferred from other institutions.

The case material under consideration is limited to 107 admissions between July 1, 1956 and June 30, 1958, which allows a minimum follow-up period of 15 months and a maximum of 39 months. It is felt that the results of treatment can be evaluated in a period of 15 months.

Among the resident patients, approximately 82 per cent are over the age of 40 and 41 per cent are over the age of 60. Approximately 40 per cent are men and more than 90 per cent are white. The age distribution of active tuberculosis closely follows the curve of age distribution.

Results

An analysis of the 107 cases admitted during the two-year period is presented in the table. These are considered in two large groups: 57 discovered at the Norristown State Hospital and 50 referred from other institutions. Those from our own hospital include only four found among approximately 2000 admissions and readmissions, giving a prevalence of 2.0/1000. There were 12 whose tuberculosis was discovered because they developed symptoms of the disease, 23 who were found through roentgenographic survey and 18 who were known inactive cases which reactivated during this period. Percentages have been calculated only for the total group because the subgroups are too small. These may be compared with percentages calculated for the 50 patients referred from other institutions.

The admission classification for Norristown State Hospital (hereafter referred to as N.S.H.) patients shows that 75 per cent were minimal or moderately advanced and only 18 per cent were far advanced. If we

TABLE 1—ACTIVE PULMONARY TUBERCULOSIS, TYPE AND RESULTS OF TREATMENT BY SOURCE OF 107 ADMISSIONS BETWEEN JULY 1, 1956 AND JUNE 30, 1958

	Discovered at Norristown State Hospital by						Referred from Other Institutions	
	Admission Film No.	Symptoms No.	Survey Film No.	Follow-up No.	Total No.	Total per cent	No.	per cent
Total	4	12	23	18	57	100	50	100
Admission Class.								
Minimal	1	0	11	5	17	30	12	24
Mod. Adv.	1	3	12	10	26	45	21	42
Far Adv.	1	6	0	3	10	18	16	32
Other	1**	3*	0	0	4	7	1*	2
Tuberculosis proved	2	7	12	7	28	49	33	66
New cases	3	11	11	0	24	42	0	0
Retreatment cases	0	0	1	5	6	11	7	14
Result of therapy								
Inactive	3	6	19	14	42	74	31	62
Minimal	0	2	16	6	24	42	18	36
Mod. Adv.	2	2	3	8	15	27	12	24
Far Adv.	0	0	0	0	0	0	0	0
Other	1**	2	0	0	3	5	1*	2
Active	0	0	1	1	2	4	12	24
sputum positive	0	0	1	0	1	2	7	14
Died	1	6	3	3	13	23	7	14
active	1	5	3	2	11	19	5	10
Far Adv.	0	2	0	1	3	5	2	4

*effusion **silico-tuberculosis

consider only those N.S.H. patients discovered by survey and follow-up of inactive cases, then only 7 per cent were far advanced. In contrast, 32 per cent from other institutions were far advanced. Six of the 12 N.S.H. patients discovered as a result of symptoms were far advanced.

Only 49 per cent of the N.S.H. patients were proved to have tuberculosis by bacteriologic or histologic methods, whereas 66 per cent of the referred cases were proved. The difference is probably related to the larger number of far-advanced cases among the latter group. The remainder of the cases were considered tuberculous on the basis of clinical and roentgenographic characteristics.

Among the N.S.H. patients, previously unknown new cases of active tuberculosis numbered 25 of the 57. If we subtract the three discovered on routine admission films, we can calculate the incidence of new active tuberculosis among resident patients to be 2.4/1000/year. In the writer's previous report,[1] the incidence was calculated to be 1.7/1000/year for the years 1955-56 for men. Later, it was found that the incidence was exactly the same for women. The difference between 1.7 and the present figure of 2.4 is not significant and approximates the incidence reported by several other groups of state psychiatric hospitals.[1] The total incidence of active tuberculosis, including new and previously known cases, is 5.9/1000/year. The incidence of active disease among approximately 300 previously known inactive cases of tuberculosis under period surveillance is 52/1000/year or roughly 20 times the incidence of new cases.

The percentage of retreatment cases was small and was equal in both N.S.H. and referred cases.

The results of therapy were significantly better among the N.S.H. cases than among the referred cases: 74 per cent of the N.S.H. patients became inactive compared to 62 per cent of the referred patients. At the time inactive status was achieved, none was far advanced in either group and a majority were minimal. At the time data were obtained for this tabulation, only 4 per cent of the N.S.H. cases were still active and only 2 per cent were still sputum positive. This is to be contrasted with the referred cases of whom 24 per cent were still active and 14 per cent still sputum positive.

Part of the difference in the percentage of persistently active cases is attributable to a slightly higher percentage of deaths in the N.S.H. group: 23 per cent as compared to 14 per cent of the transfer group. The higher number of deaths in the N.S.H. group is due to a disproportionate number of deaths among the cases discovered as a result of symptoms: 6 of 12. However, if one compares the percentage of deaths with far-advanced active tuberculosis it is found to be the same in both groups: 5 per cent for the N.S.H. cases and 4 per cent for the referred cases. It is only in the deaths associated with far-advanced active tuberculosis that the pulmonary infection is likely to have been a significant contributing factor in the demise of the patients. It is obvious that a majority of deaths with active tuberculosis today are due to non-tuberculous causes.

Discussion

The difference in the type of tuberculosis among the N.S.H. patients and those referred from other institutions is due to two factors; one is the recency with which a definite tuberculosis control program was instituted. On July 1, 1956, the program

was four years old at N.S.H., but it was more recent at the other state psychiatric hospitals. The second factor was one of selection in that following the institution of a control program at the referring hospitals, it was decided to close down their tuberculosis wards and transfer cases to N.S.H. Many of the patients had already been on treatment for one or more years and those who had responded well and finished therapy were presumably not included. For both of these reasons, N.S.H. received a group of cases from other hospitals loaded with patients who would be more difficult treatment problems. In contrast, at N.S.H. the worst cases of tuberculosis were found during the early years of the control program and were isolated. Therefore, the only types of cases which could develop were those of recent onset, whether new or reactivated known inactive cases under periodic roentgenographic supervision. Certainly, tuberculosis of recent onset may be treated successfully more often than chronic destructive disease of long duration. The latter type of case had been eliminated from the general resident patient population in previous years as a result of the first x-ray survey in 1952. Many of the tuberculous patients transferred from other institutions had the same type of chronic destructive tuberculosis found in the initial survey of the N.S.H. patients.

With the data at hand, the annual incidence of new active cases of tuberculosis may be easily calculated for a psychiatric hospital resident patient population. In a previous report,[1] the figure of 1.7/1000/year was given for men. Later the figure for women was found to be the same. The figure at this time is not significantly different: 2.4/1000/year for both sexes. If one eliminates unproved cases the figure is 1.3/1000/year. However, in view of the difficulties involved in obtaining adequate sputum specimens from psychotic patients, all patients whose clinical and roentgenographic characteristics are suggestive of active tuberculosis have been included.

These incidence figures may be compared with those for another type of captive population, the U. S. Navy, which, in 1957, had an incidence of 0.3/1000/year for proved cases of tuberculosis and a total incidence of 0.6/1000/year.[2] The naval incidence is definitely lower than the N.S.H. incidence and this is probably related to the age difference in the two populations, naval personnel being generally youthful.

Despite the fact that surveys at N.S.H. have been carried out at two-year intervals, half of the 22 new cases of active tuberculosis have been discovered as a result of the development of symptoms. Although the Navy attempts to survey its personnel at one to two-year intervals, 40 per cent of its tuberculosis cases also are discovered as a result of symptoms.[2] The law of diminishing returns makes it impossible to resurvey a given population often enough to eliminate symptom discovered cases. This is so because some tuberculosis cases are of a rather acute type (*e.g.*, pleurisy with effusion, tuberculous pneumonia, miliary or meningeal tuberculosis) and because minimal lesions are sometimes missed in survey films. The follow-up of known inactive cases of tuberculosis gives a much greater yield of active tuberculosis since the reactivation rate is 20 times the incidence of new cases. Therefore, it is mandatory that all known cases of tuberculosis be kept under constant and prolonged surveillance.

With an adequate control program, the tuberculosis problem is bound to diminish as contagion is decreased. Increased success in the treatment of tuberculosis is an important dividend of tuberculosis control and must in turn add to the control of the disease. We should see with time the manifestations of a beneficial cycle in which control and treatment beget more control.

SUMMARY

During a two-year period, 107 persons with active tuberculosis were admitted to the tuberculosis sections of a large state psychiatric hospital. Fifty were transfers from other state psychiatric institutions and 57 were discovered in the home institution. Far-advanced disease was less common among the latter and the therapeutic results were significantly better. The excellent results of treatment are attributed to an adequate tuberculosis control program which permits only cases of recent onset to come to therapy. The incidence of new active cases of tuberculosis in a captive psychotic population now approximates 2/1000/year and is approaching that which exists in the general urban population.

RESUMEN

Durante un período de dos años se admitieron 107 personas con tuberculosis activa en los departamentos de un gran hospital psiquiátrico.

Cincuenta fueron pasados de otro hospital y 57 se descubrieron en el mismo hospital. La tuberculosis muy avanzada fué menos común entre los encontrados en el hospital y los resultados del tratamiento fueron claramente mejores.

Los excelentes resultados del tratamiento se atribuyen a un control adecuado según un plan que permite sólo casos de reciente iniciación para la terapéutica.

La incidencia de casos activos nuevos de tuberculosis en una población psicótica confinada, es ahora aproximadamente de 2 x 1000 al año y se está aproximando a la que existe en la población urbana general.

RESUMÉ

Pendant une période de deux ans, 107 personnes atteintes de tuberculose évolutive furent admises dans les sections pour tuberculeux de l'hôpital psychiatrique d'un grand état. 50 étaient des transferts d'institutions psychiatriques d'autres états, et 57 furent découverts dans l'instituion locale. Les lésions furen moins fréquemment très avancées dans ce dernier groupe et les résultats thérapeutiques furent nettement meilleurs. Les résultats excellents du traitement sont attribués à un programme de contrôle tuberculeux bien conduit, qui permet que tout cas puisse être traité dès l'apparition des lésions. La fréquence des nouveaux cas de tuberculose active dans la population des asiles psychiatriques atteint maintenant 2 pour 1,000 pour une année, et approche de ce qui existe dans la population générale urbaine.

ZUSAMMENFASSUNG

Im Verlauf eines zweijährigen Zeitabschnittes wurden 107 Personen mit aktiver Tuberkulose auf die Tuberkulose-Station eines großen staatlichen psychiatrischen Krankenhauses eingewiesen. 50 wurden von anderen staatlichen psychiatrischen Abteilungen verlegt, und 57 wurden in ihrer Heimatanstalt ermittelt. Weit fortgeschrittene Erkrankungen kamen bei letzteren weniger oft vor, und die therapeutischen Resultate waren beträchtlich besser. Die ausgezeichneten Behandlungsergebnisse sind einem angemessenen Tuberkulose-Bekämpfungsplan zuzuschreiben, dem ??folge es möglich ist, daß nur Fälle mit frischer Erkrankung zur Behandlung kommen. Das Vorkommen von neuen aktiven Tuberkulose-Fällen in einer gesechlossenen psychiatrischen Population erreicht jetzt etwa das Verhältnis von 2: 1000 Jahr und nähert sich damit demjenigen, wie es bei der Gesamtbevölkerung besteht.

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ANTIBIOTICS AND SURGERY IN THE MANAGEMENT OF LUNG ABSCESS

Seventeen cases of lung abscess have been reviewed with regard to their management both medical and surgical. Importance of antibiotic therapy in these cases has been particularly stressed and appears to be the main treatment measure. The place of surgery, in their opinion, is secondary to chemotherapy.

Banerji, A., and Basu Chaudhuri, S.. K.: "Respective Place of Antibiotics and Surgery in the Management of Lung Abscess—Some Observations," *Indian J. Chest Dis.*, 3:99, 1961.

ATRIAL SEPTAL DEFECT

Ten cases of proved atrial septal defect masquerading as other forms of cardiopulmonary disease in middle-aged and elderly patients are presented. With increasing age, superimposed hypertensive or arteriosclerotic heart disease or pulmonary disease may mask an associated congenital atrial septal defect and may be the mechanism which initiates symptoms.

They stress the occurrence of atypical physical findings, transient or persistent arrhythmias, and various conduction disturbances. They emphasize that the diagnosis should be suspected in patients with such atypical findings, who also have accentuation and splitting of the second pulmonary sound, and radiologic prominence of the pulmonary vasculature and its activity. Cardiac catheterization studies are necessary for definitive diagnosis.

Sommer, L. S., and Voudoukis, I. J.: "Atrial Septal Defect in Older Age Groups," *Am. J. Cardiol.*, 7:198, 1961.

The Ciliary Mechanism in Health and Disease*

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The importance of respiratory mucosa and its secretions in maintaining a healthful state has been masked by the development of antibacterial agents, antihistaminics, and nasal anticongestants. Similarly, its importance has been ignored by surgeons and pathologists. As a primary portal of entry for bacterial, viral and other pathogenic substances, the critical respiratory tract with its defense mechanisms plays a large role in both preventive and therapeutic medicine.

By far, the major system of resistance against disease in the respiratory tract is the mucus blanket and the cilia which propel it. Since the mucus and the cilia are so closely interrelated in the physiology and pathology of the air passages, they should be studied collectively as the ciliary mechanism.

This paper will discuss the activation of the ciliary mechanism, and will cite evidence linking damage to this important defense mechanism with carcinogenesis in the respiratory tract.

Activation of the Ciliary Mechanism

That the ciliary mechanism is not controlled by a nervous system has been supported by work done by Lucas and Douglas,[1] and by Kordik, Burn, and Bulbring.[2] The former team, using an *in situ* preparation of turtle trachea were unable to demonstrate a change in rate of ciliary beat after intravenous injection of pilocarpine, epinephrine or atropine. Neither was the rate changed when the vagus and the tracheal tissue were electrically stimulated. Associating their findings with the results of physiologic studies, these investigators concluded that the motor nerves to the trachea affect only the rate at which mucus is secreted and do not change the rate at which the cilia function. Kordik's group proved the endogenous presence of acetylcholine and its synthesizing and hydrolyzing enzymes: choline acetylase and "true" cholinesterase in ciliated tissue. Acetylcholine, applied topically, increased the rate of ciliary movement. At the same time, they found no ganglion cells in the mucous membranes, and hence, concluded that the acetylcholine is produced by non-nervous tissue and serves to control ciliary movement as a local hormone.

The most promising evidence for a theory explaining ciliary activation and control comes from the work of Gosselin and Milton.[3,4] Studying the effects of 5-hydroxytryptamine (5-HT), or serotonin, on ciliary beat frequency and metabolism, they have constructed an hypothesis which is consistent with their experimental results implicating 5-HT as an activating, local hormone.

Using a stroboscopic technique for determining ciliary beat frequency of isolated, mussel gill filaments, Gosselin discovered a relationship between the administration of 5-HT (concentrations ranging from 10^{-8} to

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10^{-6} gm./ml.) and an increased beat frequency. At the same time, Gosselin found that concentrations of 5-HT greater than 10^{-4} gm./ml. tended to cause slowing of the cilia. Long exposure (greater than 30 minutes) of the ciliated gill plates to normally stimulatory concentration of 5-HT also produced inhibition of movement. These inhibitory effects may be explained on the basis of a supersaturation of the serotonergic receptor substance, producing a blocking or "persistent depolarizing" effect.[3]

A pharmacologic analog of 5-HT, bufotenine, was found to have essentially the same effects on isolated gill plate cilia as did the serotonin.[4]

Five hydroxytryptophan, a precursor of 5-HT, has been shown to increase beat frequency in ciliated gill plates, but only after a latent period. This latent period is presumably the time during which the precursor is being decarboxylated to 5-HT which then exercises its characteristic stimulatory action.[5]

Lysergic acid diethylamide (LSD-25), a known inhibitor of 5-HT also reduces the cilio-accelerator response to 5-HT in Gosselin's preparation.[3]

Using rabbit trachea, Kensler has found that 5-HT stimulates the beat frequency of the cilia—the peak rate being obtained with a concentration of 10^{-6} gm./ml.[6] Studies are now being done by Gosselin and Milton on the ciliated epithelium of postmortem human trachea specimens.

Bioassay has revealed the following facts which support a serotonergic theory of ciliary activation:

1. Gill plates contain endogenous 5-HT (0.5-1 μg./gm. of wet tissue).[5]

2. Enzymes necessary to synthesize 5-HT and to oxidize it are present in the tissue.[10]

The work performed by cilia in beating against the viscosity of the mucus blanket requires an energy source. Since cilia are unable to function for any length of time under anerobic conditions, the energy must come from an aerobic system utilizing carbohydrate (and/or fat and amino acid) substrates.

Milton[5] has noted a significant increase in oxygen consumption of ciliated gill plates during treatment with 5-HT and a similar increase with treatment using 5-hydroxytryptophan, but only after a latent period. He has also bioassayed the ciliated tissue after incubation with 5-HT and has found a depletion in glycogen in both. However, the depletion is greater in the 5-HT preparation.

The author and his associates have demonstrated an increased oxygen consumption in gill plate epithelium after incubation with ethyl alcohol. This is indicative of the ability of ciliated tissue to utilize two-carbon fragments in the production of energy via oxidative metabolism.[7]

Dinitrophenol and chlorobutanol (Chloretone), both of which are uncouplers of oxidative phosphorylation, have been found to increase oxygen consumption, as would be expected if the ciliated system were dependent upon oxidative metabolism for its energy source.[8,9]

Experiments are currently in progress which will study the effect of these compounds on the phosphorylase system in ciliated preparations.[5] It is believed that ciliary movement is brought about by an activation of this enzyme, which is responsible for the utilization of glycogen in energy metabolism. This would be similar to the already demonstrated correla-

tion in heart muscle between the activation of phosphorylase and the positive inotropic and chronotropic effects of certain sympathomimetic drugs.

It is known that the enzyme systems of oxidative metabolism are anchored to the mitochondria of the cell. These enzymatic reactions result in the formation of high energy phosphate bonds (ATP) which are used for the work of the cell—in this case, ciliary action. The presence of mitochondria in the ciliated cell, and the already cited evidence support a serotonergic-oxidative metabolism theory of ciliary activation.

Cilia in Carcinogenesis

Much evidence has been acquired recently pointing to a relationship between the ciliary mechanism and cancer of the respiratory tract. The experimental findings center around the effects of cigarette smoke and air pollutants on cilia and the mucus stream.

The function of the epithelial lining of the tracheobronchial tree is to prevent the accumulation of inhaled particulate matter. Movement of the stream of mucus is primarily related to two factors; the action of the cilia which provides the necessary propelling force, and the amount and consistency of the mucus blanket. Alteration in either the cilia or the mucus stream could conceivably affect the accumulation of foreign matter on the respiratory epithelium.

Under normal physiologic conditions, the ciliary mechanism acts to maintain the respiratory tract's freedom from harmful substances. However, under the influence of the irritants and tars found in cigarette smoke and in polluted air, changes occur which adversely affect the respiratory defenses which clear these harmful substances.

In 1939, Proetz showed that cigarette smoke affected the secretion and flow of mucus.[11] More recently, Chang found an increase in the number of goblet cells—a large percentage of which were markedly distended—in the bronchial epithelium of smokers. The length of the cilia, in smokers, was decreased and appeared irregular and worn out. Squamous metaplasia with occasional loss of ciliation also was apparent.[12]

Leuchtenberger and her associates[13] noted changes characteristic of severe bronchitis in the respiratory tracts of mice exposed to cigarette smoke. Marked proliferative changes, with loss of cilia and squamous metaplasia, accompanied the inflammatory process. The group further correlated the epithelial changes with histochemical abnormalities.

In a series of experiments, Hilding[14] has shown how carcinogenic substances could remain in contact with the respiratory epithelium for an extended period of time. He demonstrated that a substantial portion of visible smoke from cigarettes is retained within the lungs during ordinary smoking. In most instances, a certain amount of smoke returns with expiration. "This means that the air used in respiratory exchange is loaded with smoke all the way down as far as the inspired air goes. Therefore, the distribution of the deposit of the smoke must be as widespread as that of the inspired air. The deposit in the proximal portions of the tract is doubtless somewhat heavier."

The tar and other material from the smoke is deposited as a thin film upon or in the mucus blanket which normally lines the tract. Either of

two things may now determine the fate of these smoke products. They may be removed by the mucus stream, which renews itself two or three times every hour, or, because of some defect in the ciliary mechanism, these smoke materials may remain in contact with the underlying epithelium for varying periods of time.

Within the past year, Falk, Tremer and Kotin have produced evidence showing that all of the various fractions from cigarette smoke are able to decrease the rate of mucus flow by up to 40 per cent of normal. Using isolated tissue preparations, they found a persistent inhibition of the mucus stream when the epithelium was repeatedly exposed—at 20 minute intervals—to the smoke. This finding, considered in terms of the human smoker, is compatible with greater retention of particulate matter in the lungs for prolonged time intervals.

Filtration of smoke is capable of obviating the inhibitory response only when it is efficient enough to retain all particulate matter. The resulting pure gas-phase material cannot be called "smoke" as the term is generally understood.[15]

Because of the theoretic necessity that carcinogenic agents in an absorbed state be in contact with target cells for a prolonged period, interference with the normal flow of mucus must be postulated as part of the carcinogenetic mechanism. In another study, Tremer, Falk and Kotin have demonstrated that a broad spectrum of irritants from polluted air is capable of slowing the flow of the mucus stream. In certain instances, these irritants also possess carcinogenic properties. Periodic desquamation of the superficial epithelium leads to a direct apposition of carcinogenic agents to the basal layer of cells. The slowing of the mucus stream may be mediated by increases in the number and activity of the epithelial goblet cells caused by exposure of the epithelium to irritants in the air. The intensity of the histopathologic changes parallels the intensity of the abnormal physiologic response.[16]

The tar film floating upon and incorporated with the mucus blanket would meet the same obstructions encountered by the stream itself, and would tend to pause or stop at the same points as the blanket *en route* from the respiratory bronchioles to the pharynx.

Experiments by Hilding[14] show this to be true. He marked the mucus stream in the bronchioles, bronchi, trachea, and larynges of cows with India ink and noted accumulation at the following areas:

1. artificially deciliated islands
2. naturally occurring squamous islands and vocal cords
3. bronchial openings where tributary branchings arise and where the mucus stream bed narrows
4. mucus "whirlpools."

If this should occur similarly in the human smoker, the tar would not only be retained for a prolonged period in one spot, but it also would be thoroughly stirred as it lay there, thus allowing time for slow-acting, chemical reactions to go to completion.

A comparison of the effects of smog and cigarette smoke on the epithelium leads one to the conclusion that both agents can produce their effect when present in minute concentrations. If the irritating and car-

cinogenic substances present in smoke and smog should accumulate and remain upon one spot for even one-half hour, the activity of the underlying cells could conceivably be affected. If the smoker has a cigarette every half hour, that spot might not be free of tar for the entire day. The tar would be applied intimately to the mucosal cells every day for 20 to 40 years. Under these circumstances, the conditions for the production of experimental carcinoma of the skin by means of tar would be closely duplicated. The crux of the question is whether or not, in the human respiratory tract, such accumulations of tar actually exist.

The distribution of carcinoma of the lower respiratory tract corresponds well with the theoretical predictions based upon mucus studies by Hilding.[14] Bronchogenic squamous cell carcinoma tends to occur among the larger bronchi near the hilum of the lung. The hilum is the area where the mucus blanket has been gathered from a very wide stream bed to a comparatively narrow one. This is also the place where the large bronchial openings, which act as obstructions to mucus flow, are found; in addition, mucus "whirlpools" and squamous islands are located here.

The low incidence of tracheal carcinoma may be correlated with the negligible obstruction to mucus-streaming present in this passage.

Carcinogenesis seems to involve many insults of minimal duration, repeated frequently over a period of years. These conditions would prevail in the larynx where the mucus flow is retarded in its flow. Such an area would be at the level of the vocal cords, near the anterior commissure. This is where the mucus blanket comes to a standstill (because of the non-ciliated squamous epithelium of the cords), divides and passes backward along the two cords. Actually, 80 to 85 per cent of all laryngeal carcinomas occur on the cords and the majority of these occur on the anterior portion, or right at the anterior commissure.

Metastatic carcinomas from the larynx are most often found just below a tracheotomy opening on the anterior wall of the trachea. One could postulate that this would be the most likely obstruction to the ciliary stream and that detached carcinoma cells might be carried to this point and deposited in such a manner that they become transplanted and grow.[17]

This relation between carcinogenesis and obstruction to the mucus stream may be analogous to the distribution of carcinoma in the gastrointestinal tract. Tumors are most often found at areas of relative stasis where possible carcinogenic substances within the lumen may remain for some time. The cardia and pylorus of the stomach are frequent sites of carcinoma development; whereas, the small intestine, which has much less stasis, is rarely the site of carcinoma. Malignancies again increase in frequency in the large intestine, especially as the sigmo-rectum area is approached and stasis increases.

The experimental facts demonstrate that both air pollutants and cigarette smoke, by virtue of their interference with the normal function of the ciliary mechanism and their interaction with physiologic areas of mucus flow obstruction, qualify for a role in the pathogenesis of carcinoma of the respiratory tract.

SUMMARY

1. The ciliary mechanism, as a natural factor of resistance against respiratory diseases, has an important role in maintaining the health of the individual. Methods of treatment should be oriented toward sustaining the normalcy of this defense system.

2. New experimental data, supporting 5-hydroxytryptamine (serotonin) as a local hormone responsible for ciliary activation, have been presented. Serotonin is both synthesized and destroyed by ciliary tissue and can stimulate the beat frequency of isolated ciliated preparations.

RESUMEN

1. El mecanismo ciliar como factor natural de resistencia contra las enfermedades respiratorias tiene un papel importante para mantener la salud del individuo. Los metodos de tratamiento deben encaminarse hacia mantener el buen estado de este sistema defensivo.

2. Los datos experimentales mantienen la idea de que la 5-hidroxitriptamina (serotonina) es una hormona local a la que se debe la activación ciliar. La serotonina es sintetizada y destruida por el tejido ciliar y puede estimular la frecuencia de la titilación de las preparaciones ciliadas aisladas.

RESUMÉ

1. Le mécanisme ciliare, comme facteur naturel de résistance contre les affections respiratoires, a un rôle important dans le maintien de la santé de l'individu. Des méthodes de traitement devraient être orientées vers le bon fonctionnement de ce système de défense.

2. L'auteur a présenté les nouvelles données expérimentales concernant le 5- hydroxytryptamine ("sérotonin") comme hormone locale responsable de l'activation ciliaire. La "sérotonin" est à la fois synthétisée et détruite par le tissu ciliaire, et peut stimuler le rythme des préparations ciliares isolées.

ZUSAMMENFASSUNG

1. Der Flimmer-Mechanismus als ein natürlicher Faktor für die Resistenz gegen Erkrankungen der Atmungsorgane spielt eine bedeutende Rolle bei der Aufrechterhaltung der Gesundheit des Menschen. Die Behandlungsmethoden müssen so ausgerichtet sein, daß sie eine gute Funktion dieses Verteidigungssystems gewährleisten.

2. Besprechung neuer experimenteller Daten, insbesondere 5-hydroxytryptamine (Serotonie) als einem lokalen Hormon, das für die Aktivierung der Flimmerätigkeit verantwortlich ist. Serotonie wird sowohl synthetisiert, als auch zerstört durch das Flimmergewebe und kann die Geschwindigkeit des Flimmerstromes isolierter Flimmergewebspräparate anreizen.

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C-REACTIVE PROTEIN AFTER EXERESIS AND PLEUROPULMONARY DECORTICATION FOR TUBERCULOSIS

Salvati and co-workers performed the C-reactive protein test on 52 patients with tuberculosis, studying its behavior after operations for exeresis and pleuropulmonary decortication. They concluded that this test is reliable for the evaluation of a persistent activity of the disease since the CRP has been found in the great majority of the cases with postoperative complications and sequelae.

Salvati, F., Gulotta, G., and Serra, B.: "La Proteina C Reattiva Dopo Exeresi e Decorticazione Pleuropolmonare per Tubercolosi," *Ann. Ist. Carlo Forlanini*, 20:538, 1960.

CORONARY ARTERIOSCLEROSIS

A comparison of the degree of coronary arteriosclerosis and number of myocardial infarcts in 117 necropsied East Africans and 137 New Yorkers was made. In 43 subjects from each series (34 men and 9 women) matched for age and sex, the amount of coronary arteriosclerosis was generally much higher in the New York necropsy series, although the East Africans were not free from arteriosclerosis, and some overlapping occurred between the two groups. In this same matched group there were 17 myocardial infarcts among the Americans while none was found in the East African necropsy series. Comparative studies of blood and tissue lipid patterns, as well as clot lysis in the two groups, are now being carried out in an attempt to obtain other information pertaining to these findings.

Scott, R. F., Daoud, A. S., Fiorentin, R. A., Davies, J. N. P., and Coles, R. M.: "Comparison of the Amount of Coronary Arteriosclerosis in Autopsied East Africans and New Yorkers," *Am. J. Cardiol.*, 7:165, 1961.

The Cardiorespiratory Syndrome of Obesity in a Child

A Case Report with Clinical and Physiological Considerations*

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The cardiorespiratory syndrome of obesity is characterized clinically by marked obesity, somnolence, cyanosis, periodic breathing and eventually, right heart failure. Laboratory studies reveal alveolar hypoventilation, oxyhemoglobin unsaturation, hypercapnia and often secondary polycythemia. Intrinsic pulmonary disease, abnormalities of the chest bellows, lesions of the central nervous system and endocrine disturbances are not demonstrable. The syndrome is usually corrected by weight reduction.

Increasing interest in this clinical entity has been demonstrated since it was described by Sieker *et al.*[1] and Auchincloss *et al.*[2] in 1955 and subsequently coined the picturesque term "Pickwickian syndrome" by Burwell and associates[3] in 1956. Other cases and discussions have been presented.[4,5] As far as can be determined, only three cases of this syndrome occurring in children have been reported.[6,7] The purpose of this paper is to present an additional case in a child with clinical and physiological observations.

Case Report

A 10 year-old colored boy was admitted to Talmadge Memorial Hospital on June 17, 1959, because of increasing somnolence and extreme obesity. Prenatal period and delivery were normal and birth weight was eight pounds. Early childhood was uneventful except for repeated episodes of tonsillitis. At age five, tonsillectomy and adenoidectomy were performed without complications. Thereafter, his appetite became voracious and rapid gain in weight ensued. During the following year, he began to have frequent respiratory infections and by age eight, had exertional dyspnea. Lethargy and somnolence progressed steadily and six months prior to admission he was sleeping 18 to 20 hours daily, his waking hours being spent eating and watching television. His school work, which had been normal, deteriorated rapidly because of inability to remain awake in class.

Family history was significant, in that his parents and both grandmothers were obese. None of his four younger siblings was overweight.

Physical examination revealed an extremely obese 10 year-old colored boy in no apparent pain or distress. He was 140 cm. (55 in.) tall and weighed 76.0 kg. (167 pounds). Respirations were 40, regular, and noticeably shallow. He was cooperative, appeared intelligent and was fairly alert while awake, but fell asleep several times during the examination. Respiration was periodic when he was asleep. No cough was noted.

Temperature was 37°C., pulse 72 and regular, and blood pressure 110/70 mm. Hg. Cyanosis was questionable. There was no evidence of clubbing or venous distention. Retinal vessels were normal. Breath sounds were distant and a few dry rales and expiratory wheezes were audible posteriorly at the bases. Heart size could not be determined by physical examination. No murmur was heard, but the pulmonic second

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TABLE 1 — PULMONARY FUNCTION STUDIES

	Observed	Predicted Normal[12]
Respirations/min.	22	14-22
Tidal volume, ml.	162	305
Minute volume, liters/min.	3.5	4.8
Alveolar ventilation, liters/min.	1.6*	4.2
Oxygen consumption, ml./min.	164	198
Oxygen removal, ml./liter vent.	56	45
Respiratory exchange ratio	0.62	0.80
Vital capacity, liters	2.4	2.3
Inspiratory capacity, liters	2.0	1.8
Expiratory reserve volume, liters	0.4	0.6
Timed vital capacity, per cent in 1 sec.	91	83
Maximum breathing capacity, liters/min.	92	118

*Calculated by the formula (Tidal Volume — Dead Space) X Respiratory Rate, using an assumed dead space of 90 ml. Tidal volume was so small that physiological dead space, determined by the Bohr equation, was less than the dead space of the respiratory valve.

sound was accentuated. Abdominal examination was unsatisfactory. Slight pedal edema was present. Neurologic examination yielded normal findings.

Psychiatric evaluation indicated normal mentality and social adjustment.

Hemoglobin was 12.5 gm. per cent with a hematocrit of 41 per cent. Electrolytes and endocrine and metabolic studies were within normal limits. Urinalysis was normal except for 1+ albumin.

Roentgenographic examination of the chest (Figure 1) revealed enlargement of the heart in its transverse diameter, elevation of both leaves of the diaphragm, and bilateral congestion of the lungs. Skull films were normal. Bone and chronological ages were similar.

Electrocardiogram showed vertical axis, "tenting" of P waves suggestive of right atrial hypertrophy (P-pulmonale), delayed activation time in right chest leads as compared to left, and clockwise rotation around the vertical axis.

Electroencephalogram was within normal limits.

Pulmonary function studies are summarized below.

On an 800 calorie diet he had lost 7.1 kg. (16 pounds) with associated decrease in lethargy and somnolence at the time of discharge on June 28, 1959.

Strict adherence to his dietary regimen was not continued while at home and at readmission on July 22, 1959 he had lost only 1 kg. (2.2 pounds) since leaving the hospital. Interval history and repeat physical and blood examination revealed no additional finding.

Chest x-ray film (Figure 2) showed a decrease in heart size to the upper limits of normal, the diaphragm was lower with good excursion, and the lung fields were clear.

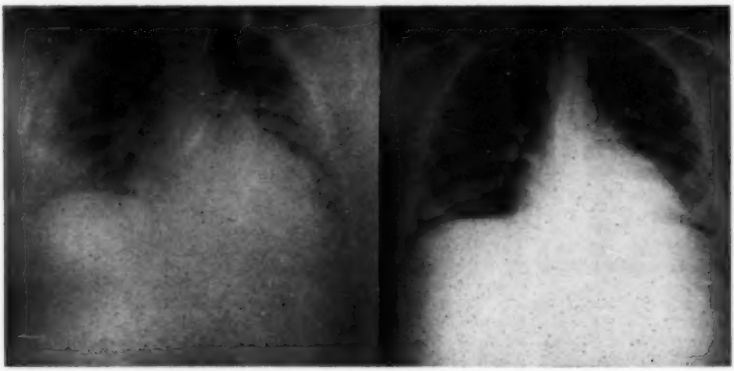

FIGURE 1 FIGURE 2

FIGURE 1: Posteroanterior roentgenogram of the chest at first admission, weight 76.0 kg., showing enlargement of heart, elevation of diaphragm, and bilateral congestion of lungs. FIGURE 2: Posteroanterior roentgenogram of the chest at second admission, weight 67.9 kg., showing decrease in heart size, diaphragm lower, and clear lung fields.

Electrocardiogram had also changed significantly. The "tenting" of P waves had regressed to within normal limits, QRS axis had shifted slightly leftward and the R wave voltage in V_1 had increased slightly. Ventricular activation time in right precordial lead was still slightly prolonged. Electrode position was not responsible for these changes since it was verified by repeated studies.

Ventilatory and blood gas studies were essentially unchanged. Cardiac catheterization was performed during this admission.

While in the hospital, adherence to his diet brought about an additional 4 kg. (8.8 pounds) weight loss and marked clinical improvement.

Again the necessity for continued weight reduction was stressed to the patient and his parents and he was discharged on August 8, 1959 to continue on a low caloric diet at home.

Methods

Respiratory status under different conditions was evaluated by continuously recording end alveolar PCO_2 using a Model 16 Liston-Becker infrared carbon dioxide analyzer and recording oxyhemoglobin saturation utilizing a Waters ear oximeter. Measurement of lung volumes, maximum breathing capacity and gas exchange were made according to the methods of Baldwin, Cournand, and Richards.[8] Cardiac catheterization was carried out as described by Cournand.[9] Ventilation-perfusion relations were evaluated according to Riley.[10] Arterial blood was collected anaerobically from an indwelling polyethylene catheter in the femoral artery. Oxygen content and capacity and carbon dioxide content were determined by the method of Van Slyke and Neill and the tensions by the Riley bubble equilibration method.[11] pH was determined at 37°C using a Cambridge Research Model pH meter. Expired air was analyzed in a micro Scholander gas analyzer.[12] All blood and gas values were required to check in duplicate.

Results

Respiratory status was quite variable. Recordings of end tidal CO_2 under different conditions are shown in Figure 3. Regular respiration with CO_2 retention and O_2 unsaturation, ranging from 87 to 92 per cent,

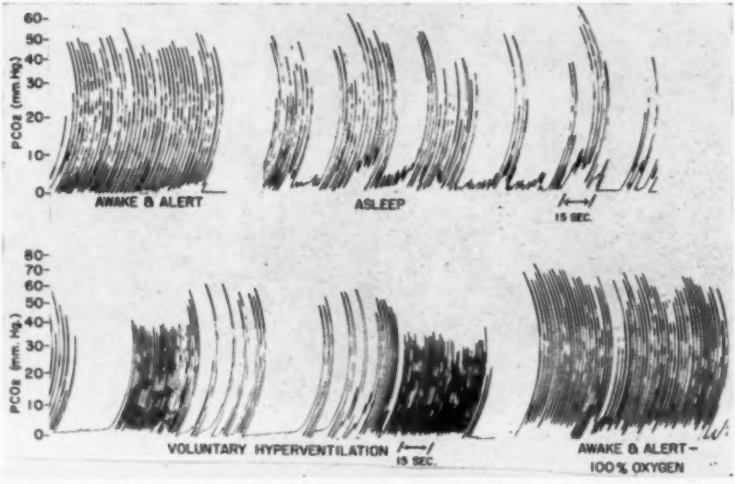

FIGURE 3: Continuous recordings of carbon dioxide concentration in expired air using infrared analyzer and Esterline-Angus recorder.

was observed when he was awake and alert. When asleep, however, he developed periodic respiration with further retention of CO_2 and reduction in O_2 saturation to 75 to 92 per cent. The latter varied in a cyclic manner. Normal values for PCO_2 and oxyhemoglobin saturation were achieved by voluntary hyperventilation which was followed by apneic periods. Administration of 100 per cent oxygen for 10 minutes corrected the oxygen unsaturation and produced an increase in the carbon dioxide tension to 70 mm. Hg.

Results of pulmonary function tests are summarized in Table 1. It is noted that tidal volume, minute volume, alveolar ventilation, and expiratory reserve volume are well below normal. Vital capacity and maximum breathing capacity are not significantly reduced. The latter was performed in a mid-respiratory position and timed vital capacity was normal. Efficiency of ventilation was not reduced as shown by the removal of 56 ml. oxygen per liter ventilated.

FIGURE 4: Lateral view of patient at second admission showing protuberant abdomen and accentuation of curves of spine.

Cardiac catheterization data (Table 2) revealed an elevated pulmonary artery pressure (65/17 mm. Hg.) which decreased significantly (42/20 mm. Hg.) when breathing 100 per cent O_2. Arterial blood analysis confirmed carbon dioxide retention and oxyhemoglobin unsaturation as previously determined pH (7.34) indicated a respiratory acidosis which became more severe (pH 7.30) during oxygen administration. Venous admixture (10 per cent of cardiac output) was greater than normal Although alveolar PO_2 was abnormally low, the alveolar-arterial oxygen difference was normal.

Discussion

Although it is generally accepted that alveolar hypoventilation is the basic physiological defect in the cardiorespiratory syndrome of obesity, its etiology and pathogenesis are debatable. The following concepts have been advanced: (1) mechanical disadvantages imposed by obesity;[14] (2) increased work of breathing caused by excessive body weight;[4] (3) inherent diminished sensitivity of the respiratory center;[2] and (4) a combination of the above factors.[5] The latter is particularly helpful as a possible explanation of why hypoventilation does not occur in all obese persons. Bedell *et al.*[15] state that hypoventilation in any patient "must be caused by lung disease, malfunction of the chest bellows, inadequate neuro-muscular coordination, or a central nervous system lesion."

In the case presented here, none of these abnormalities could be detected. In addition, no endocrine or metabolic disease was diagnosed. The postural effects of obesity resulting in mechanical interference with ventilation as described by Kerr and Lagen[14] were noticeably present in this patient (Figure 4).

Alveolar hypoventilation was shown by the presence of hypercapnia, respiratory acidosis, and hypoxemia. Oxyhemoglobin saturation determined by continuous oximeter recordings showed marked cyclic variations, especially during sleep when periodic respiration occurred. This finding might be explained by the abnormally small functional residual capacity, typically present in these cases, which may be inadequate to prevent marked shifts in blood gases during shallow respirations.[1,2]

That the patient's ventilatory capacity was sufficient for adequate blood gas exchange is shown by his ability to attain normal PCO_2 and oxygen saturation during voluntary hyperventilation.

Complete correction of the hypoxia by inhalation of 100 per cent oxygen eliminated the possibility in this patient that abnormal anatomical or physiological shunts were a cause of the oxygen unsaturation. The danger of O_2 administration in patients with chronic CO_2 retention is shown by the increase in CO_2 and decrease in pH that occurred with its use in this patient. This indicated that the respiratory center was apparently relatively insensitive to carbon dioxide and that hypoxic stimulation of the carotid body was the impetus for respiration.

TABLE 2 — CARDIAC CATHETERIZATION RESULTS

	Resting, Ambient Air	Resting 100% Oxygen (10 Min.)	Excited, Ambient Air	Predicted[13] Normal
Pulmonary artery, pressure, mm. Hg.	65/17	42/20	—	25/8
Right ventricle, pressure, mm. Hg.	—	42/7	—	25/2
Femoral artery				
Pressure, mm. Hg.	116/57	—	—	120/80
O_2, vol. per cent	13.7	15.4	15.2	—
O_2 capacity, vol. per cent	16.4	16.4	16.4	—
O_2 Hb per cent sat.	86	96	95	97
PO_2	65	100+	83	95
CO_2, vol. per cent	53.5	—	—	50
PCO_2, mm. Hg.	50	56	48	40
pH	7.34	7.30	—	7.4
Cardiac output, liters/min.	3.9	—	—	4.9
Cardiac index, liters/min/m^2	2.5	—	—	3.1
Venous admixture/% cardiac output	10	—	—	7
Alveolar PO_2, mm. Hg.	72	—	—	104
Alveolar-arterial PO_2 difference, mm. Hg.	7	—	—	9

The absence of polycythemia is unexplained in this patient. Even hypoxia of long duration, however, is not always accompanied by polycythemia.

The elevation of pulmonary artery pressure above normal is probably the result of hypoxic constriction of the pulmonary vascular bed. Probably no significant vessel change was present since the elimination of hypoxia by oxygen breathing reduced the pulmonary arterial pressure.

Cardiomegaly, frequently seen in this condition,[3] was present. Apparently, myocardial mass increases with body weight within reasonable limits, but when obesity becomes extreme the heart is not able to hypertrophy in proportion and a relative myocardial insufficiency develops. Initially, mild congestive failure was present in this patient.

His insatiable appetite was unexplained. Since this was first observed following tonsillectomy, it is interesting to speculate as to the possible psychic effects of the operation.

The more common occurrence of the cardiorespiratory syndrome of obesity in men may be explained by the fact that progesterone is a stimulus to ventilation and therefore offers some protection to the obese woman, at least during the child bearing period.[5] It is perhaps noteworthy that the three other reported cases in children were also boys.[6,7] Although the group is too small to arrive at any conclusions, if the condition is preponderant in boys during childhood, progesterone could not be the explanation.

The marked improvement that occurred following 10 kg. weight loss is strong evidence that this patient's condition can be completely corrected by adequate weight reduction. Others have observed that a critical degree of obesity exists beyond which alveolar hypoventilation occurs; apparently a small change in weight may greatly alter the patient's condition.[3]

The six year-old child with this syndrome reported by Jenab *et al.*[7] was mentally deficient and showed evidence of possible hypothyroidism. Increased appetite and rapid weight gain which occurred after an acute febrile illness indicated the possibility of a hypothalmic lesion. An additional factor which must be considered in evaluating this patient's hypoxia was the presence of a patent foramen ovale which was demonstrated at necropsy. Vigorous restriction of caloric intake did not bring about satisfactory weight reduction and the patient died. The two patients, ages seven and eleven, observed by Cayler and associates,[6] however, were greatly benefited by weight reduction. Secondary polycythemia was present in each of these three cases.

ACKNOWLEDGMENT: The authors wish to express their gratitude to Drs. David P. Hall, A. Calhoun Witham, William F. Hamilton and Victor C. Vaughan, III for their cooperation in studying this patient; to Mrs. Jerrylena Marshall and Mrs. Willie Whisenant for their technical assistance; to Mrs. Julia Byrd for preparation of the manuscript; and to the Department of Medical Illustration.

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CHANGE OF TUBERCULIN REACTION

Tuberculin reaction was successfully examined using 2000 times diluted old tuberculin one and three months after BCG vaccination in school children. The second tuberculin test (three months after vaccination) was done on the same site as the first test in the left forearm and on the different site in the right forearm. The results were read after 24 and 48 hours. On the repeated sites of the left forearm, the reaction appeared and decreased its intensity faster than the new sites of the right forearm (accelerated reaction). Morover, the reaction of the repeated sites was stronger than the new sites (augmented reaction).

Kobayashi, Y., Teramura, F., Mikawa, H., Akaishi, K., and Fukuda, H.: "Studies on the Change of Tuberculin Reaction Repeatedly Examined at the Same Site of the Skin of a BCG-Vaccinated Group of School Children," *Acta Tuberc. Jap.*, 10:84, 1960.

CYSTIC FIBROSIS OF THE PANCREAS

There are in cystic fibrosis three defects in exocrine secretions which need further study: (1) an electrolyte abnormality of sweat, saliva and tears; (2) a change in the chemical structure and physicochemical behavior of mucus secretions in duodenal fluid and, probably, through the body; (3) an increase in parotid secretory rate. The common denominator responsible for the widespread dysfunction of so many and perhaps all exocrine glands and, therefore, the pathogenesis of cystic fibrosis, has thus far escaped detection. It is generally agreed that the basic defect in this disorder, whatever its nature, is genetically transmitted. From the studies of the behavior of sweat electrolytes previously described, there is suggestive evidence that this unknown basic metabolic or enzymatic defect (perhaps concerned with the function of the autonomic nervous system) may be absent in varying degrees according to genetic endowment. This would then affect the exoression of the generalized disorder—cystic fibrosis of the pancreas—and condition the variety and severity of the clinical manifestations in different individuals.

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ROENTGENOGRAM OF THE MONTH

Edited by Benjamin Felson, M.D.

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Clinical Information

A 57 year-old Negro male first seen in this hopsital for a mild steering wheel injury to the chest, gave a past history of shortness of breath, exertional dyspnea, and occasional left chest pain for several years. He had been treated for syphilis 20 years earlier. Physical examination revealed cardiomegaly, auricular fibrillation, a grade III pulmonic systolic murmur and a grade II apical systolic murmur. Blood pressure was 150/90.

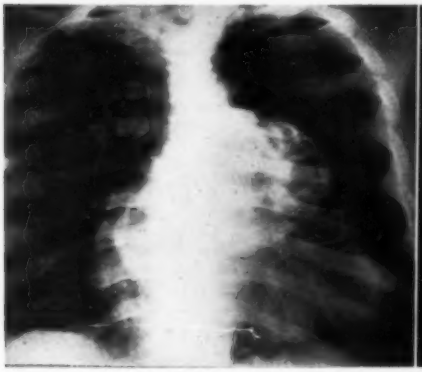

FIGURE 1

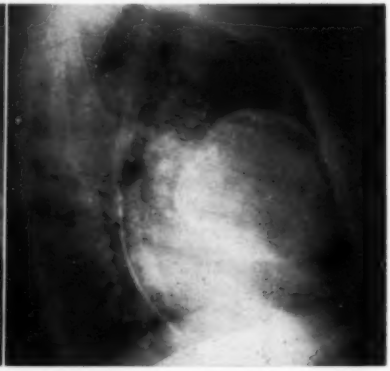

FIGURE 2

Answer: ANEURYSM OF SINUS OF VALSALVA, PROBABLY SYPHILITIC

The roentgenograms reveal cardiomegaly and a large mass at the base of the heart, outlined by calcification. Angiography revealed filling of the mass with contrast material. At operation an aneurysm originating from the right coronary sinus was found.

Aneurysm of the sinus of Valsalva may be congenital or acquired. Congenital aneurysms originate from either the right coronary or noncoronary sinus. They are usually small finger-like projections arising from the lower part of the sinus, seldom causing bulging of the external surface of the heart. They may be associated with bicuspid aortic valve or high ventricular septal defect. They are intracardiac in location. Because of their very thin walls, rupture into the heart is common, especially into the right atrium or ventricle.

Dilatation of the aortic sinuses is sometimes seen in Marfan's syndrome and in coarctation of the aorta. In coarctation the aneurysmal dilatation is probably related to hypertension and, when found, imparts a more serious prognosis, since aortic rupture or dissection may occur

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at this site. Similar complications are encountered in Marfan's syndrome.

Acquired aneurysm may be the result of syphilis, bacterial endocarditis, arteriosclerosis, or dissection of the aorta. Syphilis is the most common cause. Acquired aneurysm may originate from any one or more of the sinuses of Valsalva and is considerably larger than the congenital type. It often also involves the proximal ascending aorta.

Rupture of the aneurysm may occur into the right atrium, right ventricle, superior vena cava, pulmonary artery, or pericardium. Rupture into the lesser circulation is manifested by the abrupt onset of cardiomegaly, progressive dyspnea, wide pulse pressure and continuous murmurs and thrills. It usually signals a rapidly fatal course.

The roentgen diagnosis of unruptured congenital aneurysm is difficult or impossible without angiography. Acquired aneurysm is more readily recognized by the localized bulge or mass on the right or left side of the cardiac silhouette at the level of the aortic root, inseparable from the heart in all degrees of rotation. Syphilitic etiology should be suspected when linear calcification is seen in the ascending aorta or in the wall of the mass, especially if aortic insufficiency is present. The diagnosis can be made with more certainty if the calcification extends inferiorly into the heart and has the configuration of an aortic sinus. Abnormal pulmonary arterial pulsation indicates rupture into the lesser circulation.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

SECTION ON CARDIOVASCULAR DISEASES

Clinical and Physiologic Changes Following Surgical Closure of Atrial Septal Defect*

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and ALAN F. TORONTO, M.D.**
Salt Lake City, Utah

Surgical closure of congenital atrial septal defect has been accomplished with increasing frequency and decreasing surgical risk for the past ten years. At present, accurate surgical correction of this defect can be accomplished by several techniques at an operative mortality rate of less than 5 per cent. The prognosis and natural course of patients with atrial defects not surgically corrected is well known. Although several reports have appeared describing favorable results following surgical repair of this lesion there is need for a systematic, objective review of specific changes that take place following anatomic correction. This paper reports such a study.

Materials and Methods of Study

We have operated on a total of 42 patients with atrial septal defects utilizing the atrial well technique. One patient died, for an operative mortality of 2.4 per cent. Of the 41 survivors, the first 25 have been recatheterized to date. These 25 consecutive patients with surgically corrected atrial septal defect comprise the material for this study.

We have reviewed the pre- and postoperative clinical records of each patient. In addition to clinical evaluation of symptoms and cardiac function, each patient has had chest roentgenograms, cardiac fluoroscopic examination, electrocardiograms and cardiac catheterization, both pre- and postoperatively. An additional abbreviated, cardiac catheterization—including oxygen saturation data and, in certain cases, right ventricular and pulmonary artery pressure data—was obtained in all cases on the operating table immediately before and after closure of the defect. The pre- and postoperative physiologic studies include oxygen saturation and pressure data from the right side of the heart and the pulmonary artery as well as dye-dilution curves. Estimations of cardiac output, pulmonary flow, and systemic flow have been made pre- and postoperatively in each case.

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*Presented at the meeting of the Pacific Northwest Chapter, American College of Chest Physicians, Sun Valley, Idaho, January 8, 1960.

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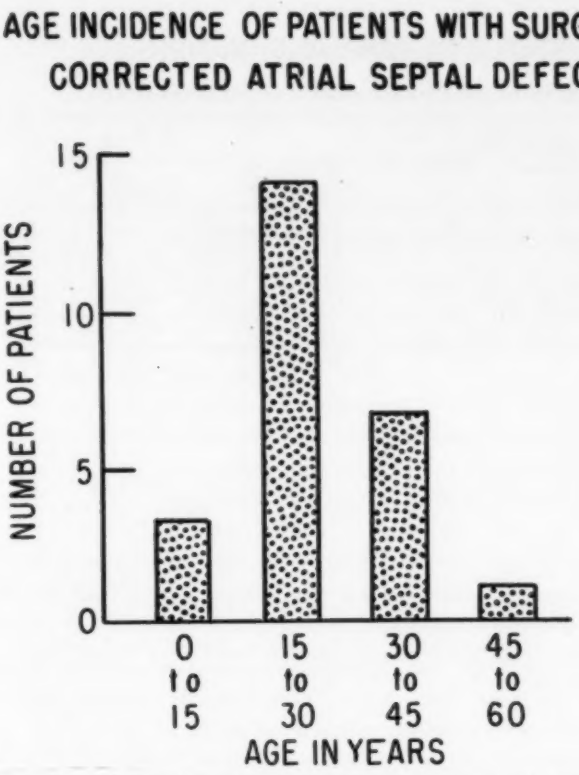

FIGURE 1: Age distribution of patients with surgically corrected atrial septal defects.

Findings

Statistical Data: The 25 patients in this series ranged from nine to 57 years of age at the time of operation (Figure 1). Twenty-one were women. All had anatomically demonstrated atrial septal defects with left to right shunts. In addition, two had associated mitral stenosis, four had anomalous connections of right pulmonary veins into the right atrium or superior vena cava, and two had anatomically significant congenital pulmonic valvular stenosis. In all these cases, the associated defect was corrected surgically at the time the atrial defect was closed. Three patients had no septal tissue between the defect and the atrio-ventricular valves (so-called ostium primum defect), and in two there was no atrial septal tissue at all (single atrium). One had constrictive pericarditis (corrected surgically before closure of the atrial septal defect), and two had surgical bronchiectasis (both corrected surgically after repair of the cardiac lesion).

Cardiac Functional Status: (Table 1) In contrast to the generally accepted impression that most patients with atrial septal defects tolerate the lesion well, we found only one who was without symptoms or had no limitation in physical activity preoperatively. Ten (40 per cent) of our patients were in functional Class III, and 4 (6 per cent) were in a

TABLE 1

STATUS OF CARDIAC FUNCTION

Before and after Surgical Closure of ASD

Functional Classification	Pre-op. Before hospitalization for Surgery		Post-op. 4-48 months after Surgery	
	No.	%	No.	%
Class I	1	4 %	23	92 %
Class II	10	40 %	2	8 %
Class III	10	40 %	0	—
Class IV	4	16 %	0	—
Digitalis				
Yes	18	72 %	0	—
No	7	28 %	25	100 %
Diuretics				
Yes	16	64 %	1	4 %
No	9	23 %	24	90 %

functional Class IV at the time of surgery. Thus, preoperatively, more than half of the patients were markedly limited in physical activity by their cardiac defect. In contrast, at their last postoperative examination (4 to 48 months after surgery) 23 (92 per cent) of these patients were *without cardiac symptoms on unlimited activity* (functional Class I). Two patients (8 per cent) were in functional Class II, experiencing symptoms only on excessive exertion. Similar evidence of change in cardiac function is attested by the observation that preoperatively 18 (72 per cent) of our patients had taken or were taking digitalis, and 16 (64 per cent) had required administration of diuretics. At their last postoperative examination, on the other hand, none of them was receiving digitalis and only one (4 per cent) received diuretics, and this only occasionally when during pregnancy she had mild ankle edema.

Auscultatory Findings: (Table 2) The typical systolic ejection murmur along the upper left sternal border was present preoperatively in all patients in our study. On a "4" basis, the murmur was considered to be of grade 2 or 3 in intensity in 22 (88 per cent) of the patients and grade 4 in the other 3 (12 per cent). In the early postoperative period, the murmur had disappeared completely in 12 (48 per cent; but on later examinations, four months or more after surgery, the murmur had disappeared completely in 22 (88 per cent). When a residual murmur persisted, it was changed considerably in intensity compared to its preoperative character; in no case postoperatively being considered greater than grade 1 in intensity.

Surprisingly, 15 (60 per cent) of our patients had a palpable systolic thrill along the upper left sternal border recorded in the preoperative notes. No patient had a thrill postoperatively. Diastolic murmurs were heard in nine (36 per cent) of our patients preoperatively, either low along the left sternal border or at the apex. All the diastolic murmurs disappeared postoperatively.

TABLE 2

CARDIAC AUSCULTATORY FINDINGS

Before and after Surgical Closure of ASD

Finding	Pre op		Post op			
			Early 6-60 days		Late >3 months	
	No.	%	No.	%	No.	%
Systolic Murmur						
None	0	—	12	48%	22	88%
1 / 4	0	—	12	48%	3	12%
2 / 4	4	16%	1	4%	0	—
3 / 4	18	72%	0	—	0	—
4 / 4	3	12%	0	—	0	—
Thrill	15	60%	0	—	0	—
Diastolic Murmur						
apical	8	32%	0	—	0	—
L.S.B.	1	4%	0	—	0	—
Intensity of P_2						
Normal	0	—	3	12%	6	24%
Slightly Increased	1	4%	16	64%	17	68%
Moderately Increased	18	72%	6	24%	2	8%
Markedly Increased	6	24%	0	—	0	—

In all instances, the second sound in the pulmonary area was distinctly split, with the second component being louder than normal preoperatively. The accented P_2 decreased noticeably in all cases after the atrial septal defect was closed. However, it was considered to be normal in only six (24 per cent) of the cases, and in two (8 per cent) it was considerably louder than normal on the last examination a year or more after surgery.

Roentgenographic Findings: (Table 3) Preoperatively, none of our patients had chest roentgenograms that were considered normal. Right ventricular hypertrophy was present in mild degree in nine (36 per cent) and in moderate or severe degree in 15 (60 per cent). Increased pulmonary vascularity, indicating pulmonary recirculation, was noted in all of the patients. The main pulmonary trunk was excessively active fluoroscopically in all patients and was considered to be enlarged on the roentgenograms in all. Over-all heart size as determined roentgenographically was considered normal in only one (4 per cent) of the patients; 5 to 15 per cent enlarged in 18 (72 per cent); and greater than 15 per cent enlarged in six (24 per cent). Postoperatively, the pulmonary vascularity decreased first and was most likely to return normal (Fig. 2). Evidence of cardiac enlargement decreased significantly in all patients who had cardiomegaly preoperatively and 19 (76 per cent) of the patients had normal-sized hearts on the last postoperative roentgenogram. The enlarged main pulmonary trunk rarely returned entirely to normal, but

TABLE 3

ROENTGENOGRAPHIC FINDINGS
Before and after Surgical Closure of ASD

Roentgen Finding	Pre op		Post op 4–48 mos. after Surg.	
	No.	%	No.	%
Right Ventricle				
Normal	1	4 %	18	72 %
+ enlarged	9	36 %	7	28 %
++ "	13	52 %	0	—
+++ "	2	8 %	0	—
++++ "	0	—	0	—
Pulmonary Trunk				
Normal	0	—	5	20 %
+ enlarged	1	4 %	16	64 %
++ "	16	64 %	4	16 %
+++ "	7	28 %	0	—
++++ "	1	4 %	0	—
Pulmonary Vasculature				
Normal	0	—	21	84 %
+ increased	0	—	4	16 %
++ "	18	72 %	0	—
+++ "	7	28 %	0	—
++++ "	0	—	0	—
Overall Heart Size				
Normal	1	4 %	19	76 %
+ increased (< 10%)	10	40 %	6	24 %
++ " (10–15%)	8	32 %	0	—
+++ " (15–20%)	4	16 %	0	—
++++ " (>20 %)	2	8 %	0	—

decreased significantly in size in 23 (92 per cent) of the cases studied (Table 3, Fig. 2).

Electrocardiographic Findings: (Table 4) Two of the preoperative and one of the postoperative electrocardiograms were unavailable, hence are not included in this review. Only two (8 per cent) of the patients were considered to have normal electrocardiograms preoperatively. Postoperatively, however, (6 to 48 months after surgery), nine (40.9 per cent) had completely normal tracings. An additional ten (45.4 per cent) postoperative electrocardiograms, although not entirely normal, were significantly improved compared to preoperative tracings. Three patients (13.6 per cent) showed no appreciable change between pre- and postoperative electrocardiograms. In none did the postoperative electrocardiogram appear more abnormal than the preoperative tracing.

As would be expected, the preoperative electrocardiograms showed a strong tendency toward right axis deviation with 16 of 23 patients showing an axis between +90° and +130° (Table 5). One with an ostium primum defect had an axis of −95°, the only patient with left axis in the group. Postoperatively there was a definite tendency to return to normal axis. All with right axis preoperatively had measurably less right axis deviation postoperatively and 6 of the 16 patients who had right axis preoperatively had axes of less than +90° postoperatively. The patient with left axis deviation also returned toward normal, his axis changing from −95° preoperatively to −60° postoperatively.

Preoperative disturbances in rhythm were seen in only one patient who had atrial fibrillation. While transient rhythm disturbances were not infrequent during the first few postoperative days, no patient had a rhythm abnormality on his last postoperative electrocardiogram. We

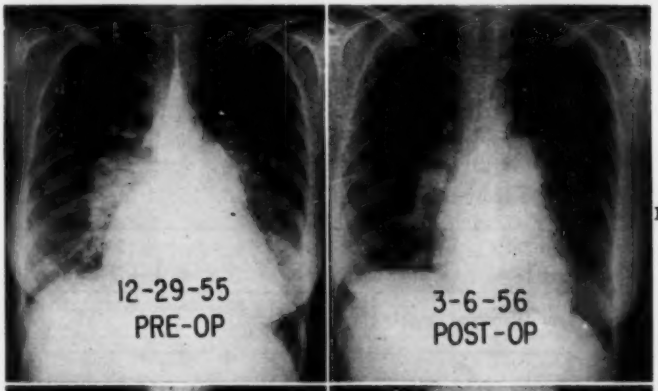

FIGURE 2A

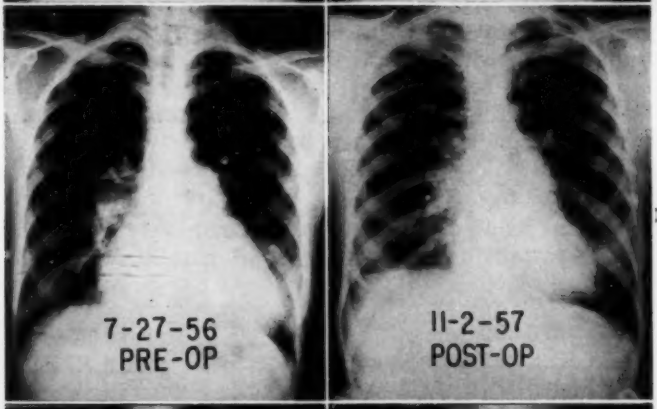

FIGURE 2B

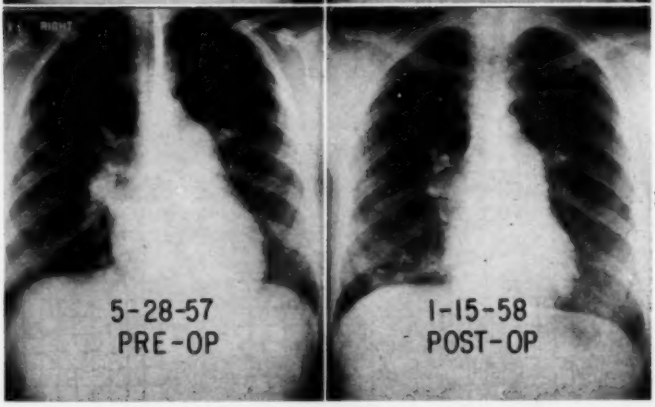

FIGURE 2C

FIGURE 2: Typical chest roentgenograms of patients with atrial septal defects before and after surgical correction. In each instance, note the change in heart size, size of pulmonary artery, and change in pulmonary vascularity.

TABLE 4

GENERAL CHANGES IN ELECTROCARDIOGRAM FOLLOWING CLOSURE OF ATRIAL SEPTAL DEFECT

Electrocardiographic change following surgery		Number	Percent
Normal tracing	pre-op.	2	8.7%
	post-op	9	40.9%
Improved, but still abnormal		10	45.4%
No change		3	13.6%
Progressively abnormal (worse)		0	0%

were interested to note that the PR interval in nine (41.0 per cent) in our series was measurably decreased in the postoperative tracing compared to its preoperative duration. The duration of the QRS complex in V_1 preoperatively varied between 0.07 and 0.12 seconds. Postoperatively, eight showed no change and two showed a slight increase in duration of QRS. The striking conduction change postoperatively, however, was a decrease in the duration of QRS in 12 of 22 patients with matched pre- and postoperative tracings.

The QRS pattern in V_1 preoperatively was rather typical, with 11 showing an rSR pattern and 8 showing a qR pattern. Thus, 83 per

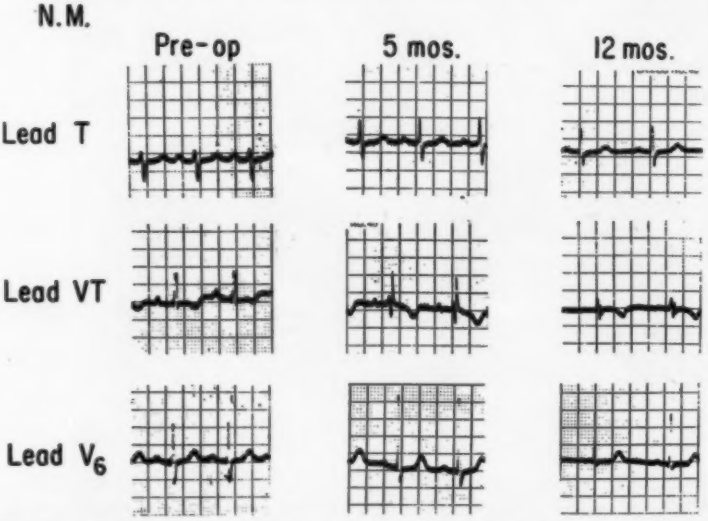

FIGURE 3: Characteristic changes in electrocardiogram of a patient with atrial septal defect, before and after surgical correction. Note the shift in electrical axis and progressive loss of electrocardiographic evidence of right ventricular hypertrophy.

cent of the patients had an abnormal pattern in V_1. Only two (8 per cent) had normal rS pattern to the QRS complex in lead V_1.

Postoperatively (Table 6) there was an impressive return toward a normal QRS pattern in this lead (Fig. 3). Four of the 11 patients with an rSR pattern showed a normal rS pattern postoperatively. Four others showed a striking decrease in the height of the R wave while only two showed no change. In the qR group, three (38 per cent) of the eight showed a return to a normal rS pattern. Only one patient showed no appreciable change while four showed decrease in the amplitude of the R wave.

Cardiac Catheterization Data: Preoperatively, all patients had a significant left to right shunt of blood at the atrial level. In most cases this shunt was large, causing the pulmonary flow to be approximately two and one-half to three times as great as the systemic flow (Fig. 4). In three cases there was also evidence of a right to left shunt in association with the larger left to right shunt. Postoperatively the shunt was completely obliterated in all but one case. In this one case, a small left to right shunt remained with the pulmonary flow being 1.2 times the systemic flow. Dye-dilution curves as well as oxygen saturation data were used to identify and quantitate the shunts both pre- and postoperatively.

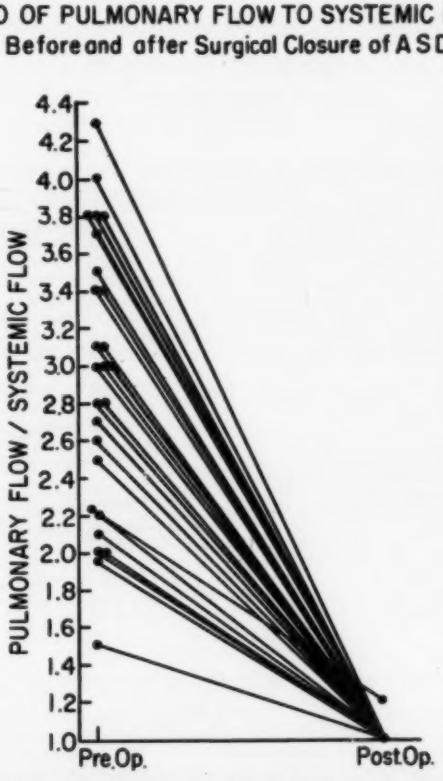

FIGURE 4: Effect of surgical closure of atrial septal defect on the intracardiac shunt.

TABLE 5

ELECTRICAL AXIS OF ELECTROCARDIOGRAMS BEFORE AND AFTER SURGICAL REPAIR OF ATRIAL SEPTAL DEFECT

Axis	Out of 23 Pre-op. tracings	Out of 24 Post-op tracings
+90° to +130°	16	10
+60° to +90°	3	7
0 to +60°	3	6
Less than 0° (left axis)	1	1

Right ventricular systolic pressure was above 30 mm. of mercury in all but two of our patients preoperatively. In most cases, the pressure was only mildly or moderately elevated, but in ten (40 per cent) of the cases it was over 40 and in four (16 per cent) it was over 60 mm. of mercury before surgery. Postoperatively all patients but one had a drop in right

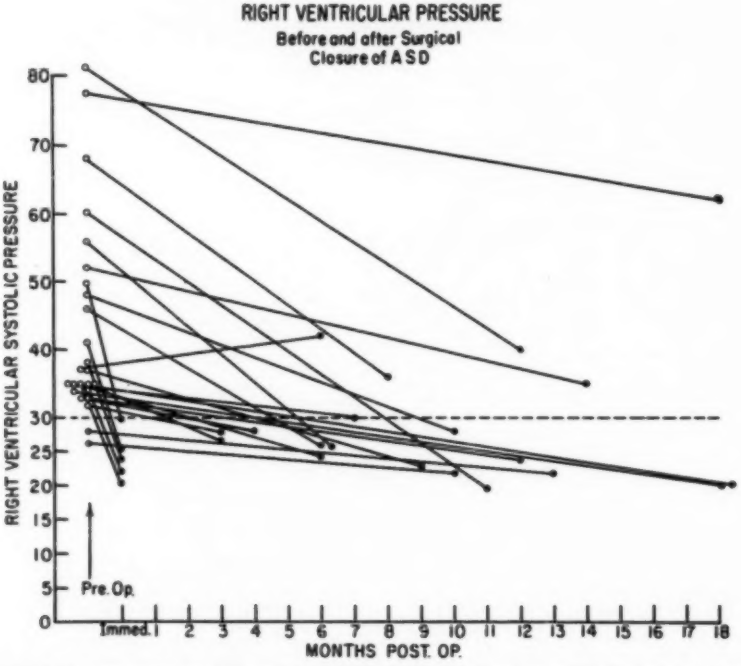

FIGURE 5: Changes in right ventricular pressure following surgical closure of atrial septal defects. The time of the postoperative study does not indicate time required for pressures to return to normal, but simply denotes the time interval beween surgery and recatheterization.

TABLE 6

QRS CHANGES IN LEAD Vi BEFORE AND AFTER SURGICAL REPAIR OF ATRIAL SEPTAL DEFECT

QRS Findings	Pre operative Number of Tracings	Post operative Number of Tracings	Post operative R wave changes			
			No Change	Increased	Decreased	to rS
PATTERN:						
rSR	11	9	2	0	4	4
qR	8	5	1	0	4	3
Rs	2	2	0	0	2	–
rS	2	8	–	–	–	–
DURATION:						
Range	0.07 to 0.12	0.06 to 0.12	8	2	12	
Mean	0.085	0.078				

ventricular pressure. Indeed, postoperatively 20 (80 per cent) of the patients had right ventricular pressure of 30 mm. of mercury or less. Only one patient had significant right ventricular hypertension after closure of the atrial septal defect (Fig. 5). The physiologic evaluation of cardiac catheterization data indicated significant abnormality in cardiovascular hemodynamics in all cases of atrial septal defects preoperatively, while postoperatively the conclusion of physiologic evaluation was "hemodynamically normal" in 22 (88 per cent).

Comment

We have been particularly interested to note the rather serious alterations in functional status and physiologic data in this group of unselected patients with atrial septal defects. In common with many others, we had previously considered this lesion to be a relatively benign one, usually quite well tolerated by the patient. Our preoperative data, however, must be accepted as strong evidence against this concept.

It seems apparent from these studies that successful repair of an atrial septal defect results in prompt and essentially complete physiologic as well as anatomic cure of the lesion. It will be many years, of course, before data will be available to demonstrate whether a patient's life expectancy becomes normal after closure of an atrial septal defect, but certainly with hemodynamically normal hearts demonstrated in 88 per cent of the patients after repair of such defects, it would seem likely to expect an essentially normal future course.

In view of the low mortality rate (2.4 per cent), high rate of complete surgical correction achieved (96 per cent), and complete return of all physiologic data to normal limits in so many patients (88 per cent), we must conclude that atrial septal defect can most assuredly be classed as a surgically correctable, readily curable cardiac defect. In our opinion, it must now be considered as correctable as patent ductus arteriosus and coarctation of the aorta.

SUMMARY

Twenty-five consecutive patients with atrial septal defects have been carefully evaluated clinically and by cardiac catheterization both before and after surgical repair of the defect. Critical review of the data indicates that successful closure of an atrial septal defect results in prompt and significant improvement in symptoms, physical findings, objective laboratory tests, and cardiovascular dynamics. It appears that physiologic abnormalities return to normal or near normal promptly after the defect is closed. Thus, atrial septal defect appears to be a readily curable lesion.

RESUMEN

En veinticinco casos consecutivos de defecto de tabique auricularse ha hecho una valoración tanto clínica como por la cateterización cardiaca exactamente antes y después de la reparación del defecto. La revisión crítica de los datos indica que el cierre del defecto produce una mejoría inmediata y significativa de los síntomas, de los hallazgosfísicos, de las pruebas de laboratorio y de la dinámica cardiovascular.

Parece que las anormalidades fisiológicas vuelven a lo normal o se aproximan a ello después del cierre del defecto. Por tanto, la intercomunicación auricular parece ser una lesión fácilmente curable.

RESUMÉ

25 malades atteints de malformations du septum auriculaire ont été soigneusement examinés cliniquement et par cathétérisme cardiaque à la fois avant et après réparation chirurgicale de la malformation. Une revue critique des données indique que la fermeture satisfaisante d'une malformation de la paroi auriculaire implique une amélioration rapide et nette des symptômes, des constatations physiques, des tests objectifs de laboratoire et de l'hémodynamique. Il semble que les anomalies physiologiques reviennent à la normale ou au voisinage de la normale rapidement après que la malformation ait éte traitée. C'est pourquoi la malformation de la paroi auriculaire semble être une lésion parfaitement curable.

ZUSAMMENFASSUNG

25 Patienten mit Vorhofseptumdefekten wurden klinisch und mit Herzkatheterisierung eingehend untersucht vor und nach chirurgischer Intervention. Eine kritische Auswertung der gewonnenen Ergebnisse zeigt, dass der erfolgreiche Verschluss eines Vorhofseptumdefektes zur schnellen und deutlichen Verbesserung der Symptome, physikalischen Befunde, Laboratoriumsergebnisse und Haemodynamik führt. Die physiologischen Verhältnisse scheinen unmittelbar nach dem Verschluss des Defektes zur Norm oder annähernd zur Norm zurückzukehren. Ein Vorhofseptumdefekt ist daher offenbar ein gut heilbarer Herzfehler.

THORACIC SURGERY AT HIGH ALTITUDE

The author reports his experience with 17 lung resections in the Obrero de Huariaca Hospital (9570 feet above sea level), and one case of lung resection for tuberculosis performed at the Policlinico Obrero de Cerro de Pasco at an altitude of 14,500 feet above sea level, which probably is the only such experience in the world.

The conclusions of this work are as follows:

1. In this series of 17 cases, there were two operative accidents, seven cases of thoraco-pulmonary complications, four instances of extrapulmonary complications and two cases of postoperative death. Pulmonary hydatidosis and pulmonary tuberculosis comprise the largest number of operated cases. Incidence of pulmonary malignancy was minimal.

2. Thoracic surgery may be performed at high altitudes without more risk than at sea level. High altitude does not interfere with successful thoracic surgery. Critical selection of cases, careful preoperative study, proper anesthesia, surgical skill and good postoperative care are mandatory safeguards of the favorable outcome in every case.

The results of this series justify the practice of pulmonary resections in institutions at high altitudes.

Vallalobos Pereda, J.: "Thoracic Surgery at High Altitude," *Prov. of Yauli Med. Assoc. Rev.*, V:2, 1960.

CLINICAL AND EXPERIMENTAL APPLICATION OF DIAPHRAGMATIC GRAFTS FOR RECONSTRUCTIVE SURGERY

The authors have utilized pedicled grafts from diaphragm in experimental plastic surgery for thoracic aorta defects. The results to date indicate that diaphragmoplasty might be used not only in esophageal or cardiac aneurysm surgery, but also for the correction of lateral defects in the descending aorta if the vascular suture is potentially in danger of narrowing its lumen.

Ostroverchov, G. E., and Skobelkin, O. K.: "Clinical and Experimental Application of Diaphragmatic Grafts for Reconstructive Surgery." *Chest Surgery (USSR)*, 85:99, 1960.

Anticoagulant Treatment in Acute Coronary Occlusion with "So-Called" Ischemic Pattern*

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Since the introduction of the anticoagulant drugs for the treatment of acute myocardial infarction, numerous reports[1-6] indicate that the frequency of thromboembolic complications is less and that mortality has been reduced. The Committee on Anticoagulants of the American Heart Association in 1947-48 reported that the mortality in a series of 1,030 cases of myocardial infarction treated with anticoagulants was 15 per cent as compared to 24 per cent in a "control" or untreated series and that the thromboembolic complications showed an even more favorable reduction—11 per cent against 25 per cent in the untreated "control" series. Such comparative success naturally raised the question whether or not anticoagulants should be used routinely in all cases of myocardial infarction, except where specifically contraindicated. In patients with apparent impending myocardial infarction, anticoagulant therapy has been recommended. Nichol *et al.*[6] report favorable results from the prophylactic anticoagulant treatment of patients with impending coronary occlusion.

Others,[7-10] however, have thought that these drugs should be used only when the attacks are clinically severe. Russek and co-workers[7] have divided cases of myocardial infarction into "good" and "poor" risks, which they believe can be done at the time of first examination. They

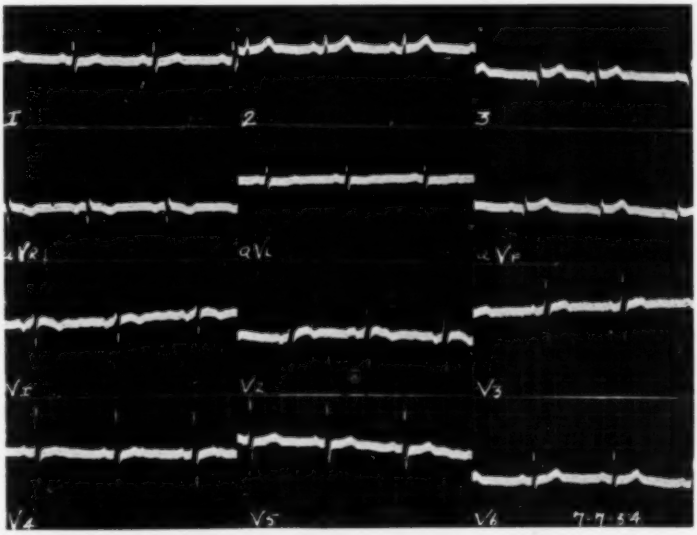

FIGURE 1 (Case 20): Electrocardiogram made July 7, 1954, several days before sudden death.

*From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

classify as "good" risks those patients who have never had a previous infarct and who "do not have intractable pain, extreme or persistent shock, significant cardiac enlargement, gallop rhythm, congestive heart failure, auricular fibrillation or flutter, or ventricular tachycardia or intraventricular block, and who do not have diabetic acidosis or other states predisposing to thrombosis." In their group of 511 "good" risk cases who did not receive anticoagulant treatment and who were watched closely for thromboembolic complications, the latter occurred in only 3.7 per cent of cases and were all of a mild nature. Of this untreated group of 511 cases, there were 18 deaths (3.5 per cent), and analysis of the causes yielded no evidence that anticoagulant treatment would have significantly reduced the mortality. Russek *et al.*[7] stress the fact that they selected only cases having typical clinical onset and classic electrocardiographic patterns and that abnormal Q waves were a prerequisite for diagnosis. The conclusions of these authors were based on the infrequency of thromboembolic complications and rather low mortality in their so-called "good" risk cases. However, others do not agree that "good" risk cases can be diagnosed as such soon after the initial onset of symptoms and point out the difficulty at times of determining whether a course is going to be mild. Not uncommonly, mild cases suddenly become severe and even prove fatal a few days later.

In our experience, this change in status occurs so often that it cannot be considered uncommon. Even patients with a so-called "ischemic pattern" in whom there are T wave inversions without QRS complex changes in the electrocardiogram, and in whom the prognosis as a group is favorable, not infrequently develop an extension of the myocardial lesion leading to fatal results in some and serious complications in others. Cutts, Merlino and Easton[11] studied the case histories of 69 hospitalized patients with chest pain at rest that lasted more than 15 minutes and with electrocardiograms that showed deep inversion of the T waves, particularly in the precordial leads but without QRS complex changes. After a follow-up period of about four years, there were 24 deaths, of

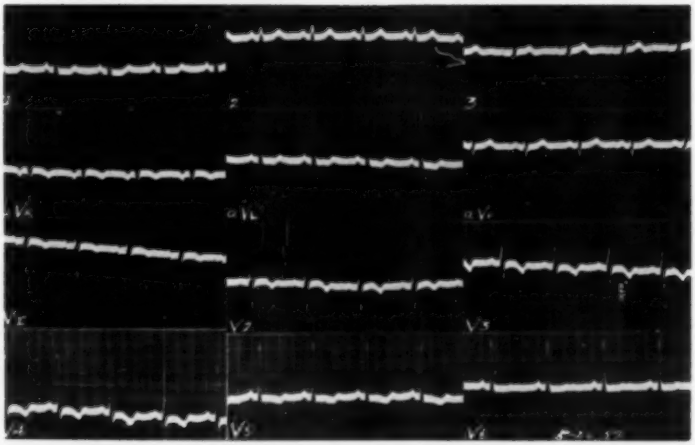

FIGURE 2 (Case 17): Electrocardiogram made May 20, 1957, 11 days before anteroseptal infarction complicated by acute pulmonary edema.

TABLE 1

	Age	Sex	Previous Hypertension	Heart Size Orthodiagram	Arrhythmia	Original Electrocardiogram	Interval	Infarction and Complications
1	58	M	None	Normal	—	T diphasic V_6	3 da.	Posterolateral
2	61	M	None	Plus 12%	Wenckebach periods during infarction	T inversion 2 and 3	2 da.	Posterior
3	65	F	170/100	Normal	—	T inversion 1, V_5 and V_6	2 da.	Anterior; cerebral embolism
4	51	M	180/100	Plus 24%	—	T inversion 1, V_2 to V_6	1 da.	Anterior
5	68	M	170/90	Normal	—	T inversion V_1 to V_4	3 wks.	Anterior
6	73	F	190/100	Plus 33%	Parox. atrial tachy. during infarc.	T inversion 1, V_5 and V_6	6 da.	Anterior pulmonary embolism
7	45	M	None	Plus 10%	Parox. atrial tachy. during infarc.	T diphasic 1, V_1 to V_5	5 da.	Anteroseptal
8	65	M	None	Normal	—	T inversion V_2 to V_6	7 da.	Posterior
9	63	M	150/100	Normal	—	T flat 1, V_2 to V_6	6 hrs.	Died soon after admission to hospital
10	68	M	None	Normal	—	T inversion V_2 and V_6	11 da.	Anterior
11	47	M	None	Normal	—	T inversion V_1 to V_6	3 da.	Anterior
12	43	M	None	Normal	—	T inversion V_1 to V_4	10 da.	Anterior
13	74	M	Labile	Normal	—	T flat V_5 and V_6	9 da.	Anterolateral
14	78	M	None	Slightly enlarged (chest film)	—	T inversion 1, V_5 to V_6	1 wk.	Anterior
15			None	Normal	—	T inversion 1, V_4 to V_6	8 da.	Anterior infarction
16	49	M	None	Normal	—	T diphasic 1, 2, V_6	2 da.	Anterior
17	65	F	Labile	Normal	—	T inversion 1, V_1 to V_5	11 da.	Anterior pulmonary edema
18	44	M	None	Normal	—	T inversion 1, V_4 to V_6	4 da.	Died 15 minutes after admission to hospital
19	45	F	190/110	Normal	—	T inversion 1, V_5 to V_6	Several hours	Anterior
20	60	M	158/70	Normal	—	T inversion lead 1, diphasic V_2 and V_3, flat V_4	2 da.	Died night of admission to hospital
21	55	M	None	Normal	—	T inversion 1, V_5 to V_6	8 da.	Anterior infarction
22	71	M	180/100	Normal	—	T diphasic V_4 to V_6	13 da.	Posterior infarction; Died

None had history of previous congestive heart failure or heart block and only one had history of mild diabetes and one history of an ischemic change one year previously.

which 14 were due to heart disease, chiefly myocardial infarction; seven of these occurred during the first year. In all autopsied cases there was a high degree of atheromatous narrowing of the coronary arteries. Our study, however, is concerned with the *early* follow-up of this type of patient, especially those whose symptomatology suggested myocardial infarction, who showed T wave abnormalities but no QRS complex changes in the electrocardiogram.

This communication gives the pertinent findings of a study suggesting that: (1) it is not possible to determine on first examination whether a patient suffering an acute coronary occlusion is a "good risk." Even patients with a so-called "ischemic pattern," for whom the group prognosis is comparatively good, not infrequently develop into "poor risk" cases; and (2) anticoagulant treatment is often, but not always, of value in preventing extension of the lesion in patients with the so-called "ischemic pattern."

Our study deals with a group of 22 patients of approximately 200 with clinical symptoms of myocardial infarction that have been observed by us in private practice during the past five years whose initial attack appeared to be mild. In these 22 the clinical course shortly thereafter became severe, with fatal results in some instances. While the clinical picture strongly suggested myocardial infarction, the electrocardiogram showed T wave changes only and, in a few, T wave changes with minor RS-T segment deviation. Inasmuch as no significant Q waves were present, these attacks could not be *electrocardiographically* classified as infarctions. Whether some or all with persistent T wave inversion only had an actual infarction cannot be answered with certainty, although the clinical history was strongly suggestive of an infarction. The duration and severity of the pain was much greater than that expected of patients with so-called "pilot angina" or coronary insufficiency that frequently herald an oncoming myocardial infarction; but the absence of prolonged shock and other signs or symptoms frequently observed in extensive infarctions suggested that the attack was a "mild" one. This

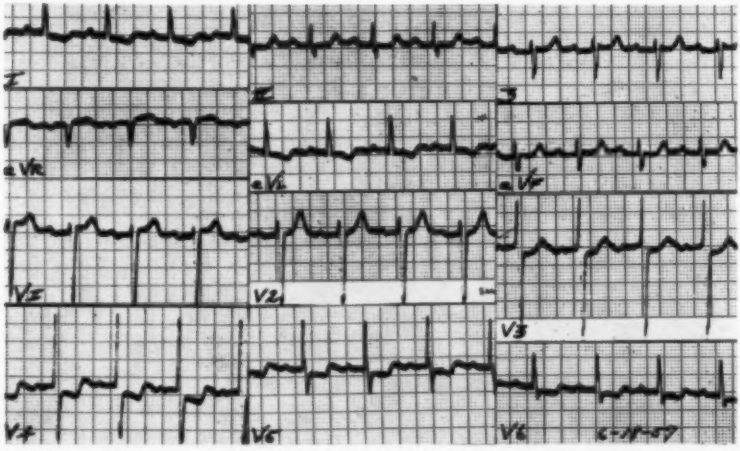

FIGURE 3 (Case 14): Electrocardiogram made June 18, 1957, shortly after severe bout of chest pain.

type of case is common, and in our experience these patients, as a group, have a favorable prognosis; but not infrequently this first bout of pain is followed by a second, after an interval of a day to several weeks, and then the typical electrocardiographic pattern of myocardial infarction develops. This sequence of events, sometimes with catastrophic results, has been observed by us often enough in patients not included in the present study to warrant the statement that it is not uncommon.

Our group of 22 patients offers an important indication of the difficulty of accurately predicting the future course of patients who have suffered an acute coronary occlusion and in whom the electrocardiogram may or may not show the typical pattern of myocardial infarction. Furthermore, the majority did not receive anticoagulant treatment. An example is Patient 3 (see Table 1) who had a moderate hypertension but was free from symptoms until the sudden onset of severe and prolonged chest pain that was diagnosed as acute coronary occlusion. Because the electrocardiogram showed T wave changes only, the attack was not considered severe and neither hospitalization nor anticoagulants were advised. Several days later she had another bout of chest pain, when hospitalization and anticoagulants were advised; but before the latter could be started she developed a cerebral embolus with motor aphasia and right sided hemiplegia. To date she has remained a hopeless invalid. The same sequence of events so far as multiple bouts of pain are concerned is further exemplified in the following case reports:

Case 20: Patient, J. M., aged 60, was examined on July 7, 1954 because of severe and prolonged chest pain the night before. Previously he had been in good health. Figure 1 shows his electrocardiogram made on July 7, 1954. Because of the severity and duration of his pain and in spite of comparatively slight changes in his electro-

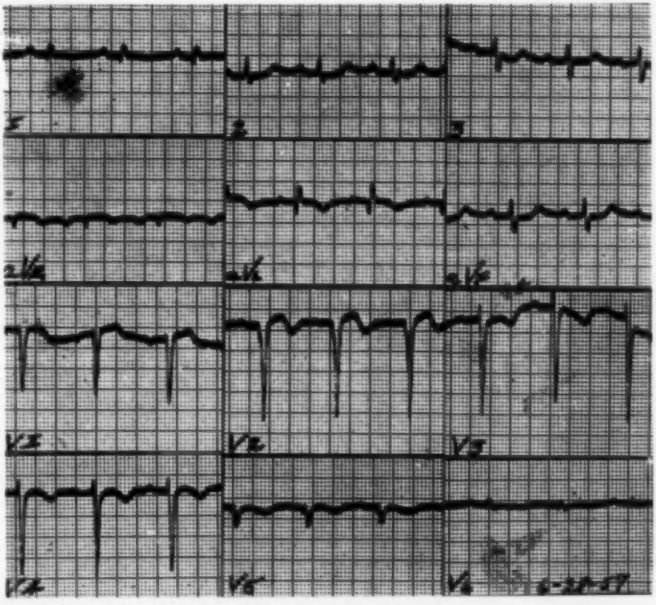

FIGURE 4 (Case 14): Electrocardiogram of same patient as in Fig. 3 made on June 28, 1958 after third severe attack of chest pain.

cardiogram, he was advised to enter the hospital, but refused. During the night of July 8, 1954 he again had severe chest pain and decided to enter the hospital; he was admitted to the Hospital of the University of Pennsylvania on the following night, July 9, 1954, in comparatively good condition and free from pain. He was started on anticoagulants, but at 2:00 a.m. on July 10, 1954 he was found dead in bed.

Case 17: B. T., a white woman, aged 65, was examined in the office on May 20, 1957 because of severe attack of substernal pain the night before. Her electrocardiogram showed the so-called ischemic pattern (Figure 2) and she was, therefore, strongly urged to enter the hospital for anticoagulant treatment. She refused until May 31, 1957, when she was admitted to the Hospital of the University of Pennsylvania because of severe chest pain associated with acute pulmonary edema. The electrocardiogram made after her admission showed an acute anteroseptal infarction. After a few stormy weeks she recovered sufficiently to be discharged on July 5, 1957, although she remained fairly dyspneic on slightest exertion.

Case 14: S. S., a white man, aged 78, first experienced severe chest pain on June 18, 1957. Hospitalization was advised but refused. Figure 3 is the electrocardiogram made that day. Several days later he had another severe bout of chest pain and further changes were seen in his electrocardiogram, although abnormal Q waves were not present. He still refused to enter the hospital, but several days later did consent and was admitted to the Hospital of the University of Pennsylvania. Soon thereafter he had another bout of pain. This time his electrocardiogram showed an infarction pattern involving the anterior wall of the left ventricle (Figure 4); the attack was associated with severe shock. Nevertheless, after a stormy course complicated by a cerebral embolus, he improved sufficiently to be discharged on July 26, 1957.

Case 22: E. C., a white woman, aged 72, was admitted to the Southern Division of the Albert Einstein Medical Center on May 31, 1958. She was a mild hypertensive and had a history of angina pectoris of one year's duration. On the morning of admission she had severe substernal pain associated with marked cyanosis and dyspnea, and soon thereafter she collapsed. Her pulse and blood pressure were barely perceptible but she soon rallied and her blood pressure gradually rose to 120/80; on admission to the hospital, several hours later, it was 150/70. Figure 5 is her electrocardiogram made on admission, when she appeared to be in excellent condition, in no pain and with no evidence of shock. A portable x-ray film examination of her chest showed that her heart was not enlarged but that there was arteriosclerosis of the aorta. Her laboratory findings, including blood sugar, were entirely negative. Anticoagulants were started despite her apparently excellent condition. An electrocardiogram made on June 2, 1958 showed considerable improvement (Figure 6). She continued to be free from pain until June 13, 1958, 13 days after the initial bout of pain, when she noted slight discomfort in the chest at 12:45 p.m. At 5:45 p.m. that day she had a severe bout of pain and one hour later she suddenly died. Figure 7 is the

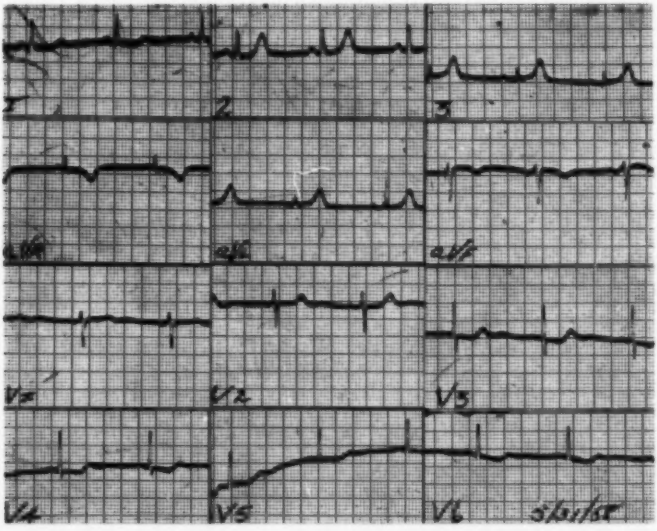

FIGURE 5 (Case 22): Electrocardiogram made May 31, 1958 shortly after admission to hospital and about two hours after severe attack of substernal pain associated with severe shock. The blood pressure was 150/70 when the tracing was made.

electrocardiogram made shortly after the 5:45 p.m. bout of pain. Necropsy examination showed a severe grade of coronary sclerosis in all vessels, with occlusion of the right coronary and left circumflex arteries; there was an acute myocardial infarction involving the posterior aspect of the left ventricle. There was no evidence of pericardial effusion or hemorrhage.

Discussion

It is well recognized by all clinicians who have had a long experience in the management of patients with coronary disease that once these patients develop "coronary" pain without apparent provocative cause or a change in the previous "stable" angina pectoris, a subsequent myocardial infarction is not uncommon. Therefore, in our opinion, when a patient has an attack of persistent pain suggesting myocardial infarction he must be treated as if he had an infarction, whether the electrocardiogram shows the typical pattern or not.

Some time ago Russek attempted to indicate that when a clear cut diagnosis of myocardial infarction is made he could differentiate between good risk and bad risk patients. Others have been unable to make this differentiation early in the history of the case and the present study would strongly suggest that in many cases the differentiation cannot be made early. In the past five years the author has observed 22 patients, from approximately 200, who had clinical evidence of myocardial infarction but whose electrocardiogram did not show the typical pattern until later, after several days to three weeks, when the typical pattern was seen after a second bout of pain, which proved fatal in some of these 22 cases.

Analysis of the pertinent facts listed in Table 1 would indicate that these patients, even if infarction had been present from the onset, as we believe, would fall into Russek's category of "good" risks, with a few possible exceptions. Two cases (18 and 20) were found dead in bed shortly after admission to the hospital, the probable cause being myocardial infarction. Ten cases (3, 5, 6, 8, 11, 14, 15, 17, 18, and 20) received no anticoagulant treatment, seven because hospitalization was refused, two because their condition was not considered serious enough, and one because of the contraindication of a history of duodenal ulcer. The majority of our cases were hospitalized and except for four cases (8, 10, 21, and 22), who suffered infarctions while receiving adequate anticoagulant treatment, the remaining patients suffered another bout of pain and developed the typical infarction pattern in the electrocardiogram before anticoagulants were started or could be considered sufficient. Thus, an extension of the original lesion may occur in spite of adequate anticoagulant treatment. Nevertheless, comparatively few in this group of patients studied, who received adequate anticoagulant treatment during the acute phase, went on to develop another attack of pain and the typical infarction pattern in the electrocardiogram. In our opinion, prophylactic anticoagulant treatment may prevent an extension of the myocardial lesion in many but not in all of those patients who have symptoms suggestive of acute myocardial infarction but whose electrocardiograms show no definite infarction pattern. Furthermore, the frequency with which the cases reported here proceeded

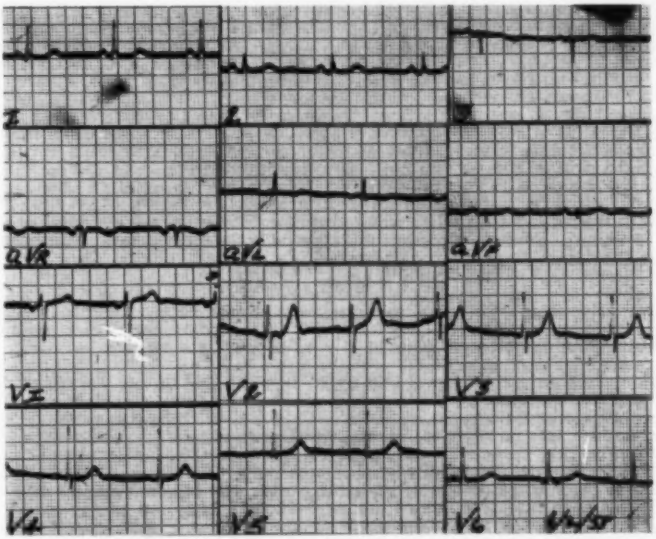

FIGURE 6 (Case 22): Electrocardiogram made two days later.

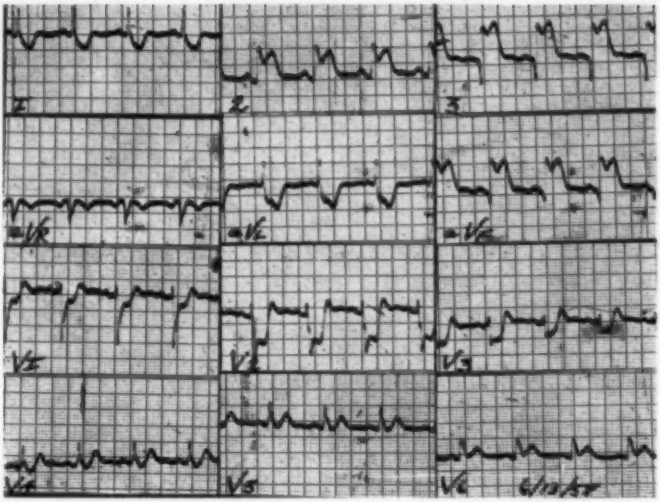

FIGURE 7 (Case 22): Electrocardiogram made June 13, 1958, 13 days after initial attack of pain and shortly after a severe attack of chest pain and one hour before sudden death.

to have major infarctions, sometimes with fatal results, demonstrates the difficulty of accurate evaluation at the onset of an attack of the seriousness of an acute coronary occlusion with or without electrocardiographic evidence of a definite myocardial infarction. Extension of the initial lesion occurs often enough to warrant healthy respect for all cases of acute coronary occlusion.

SUMMARY AND CONCLUSIONS

1. During the past five years, approximately 200 cases were observed whose clinical history strongly suggested myocardial infarction, but the electrocardiogram showed T wave changes only and, in a few instances T wave changes and minor RS-T segment deviation. In 22 of these patients, after an interval of a day to several weeks, the initial bout of pain was followed by a second, with the development of the typical infarction pattern in the electrocardiogram.

2. Ten of the cases received no anticoagulant treatment—seven because hospitalization was refused, two because their condition was not considered serious enough, and one because of a history of duodenal ulcer. Eight other cases developed the infarction pattern in the electrocardiogram before anticoagulants could be started or given in sufficient amounts. There were five (28 per cent) deaths in this group.

3. The majority of the approximately 200 cases were hospitalized and given anticoagulant treatment. Four of them developed the pattern of myocardial infarction in the electrocardiogram. Two (50 per cent) of these four died.

4. An extension of the myocardial lesion may occur in spite of anticoagulants; but it is our impression that this took place in our subjects most often when anticoagulants were withheld or not given in sufficient amounts.

5. It is not possible to predict accurately the future course of patients who have suffered an acute coronary occlusion and in whom the electrocardiogram may or may not show the typical infarction pattern.

RESUMEN

1. Durante los últimos cinco años, se observaron aproximadamente 200 casos cuya historia clínica sugirió fuertemente infarto del miocardio pero el electrocardiograma mostró solamente cambios en la onda T y en pocos casos cambios en onda T y desviación menor del segmento RS-T.

En 22 de estos enfermos después de un intervalo desde un día a varias semanas el dolor inicial fue seguido de un segundo dolor con aparición del cuadro típico de infarto en el electrocardiograma.

2. Diez de los casos no recibieron tratamiento anticoagulante-siete porque rehusaron hospitalización, dos porque no se consideró bastante serio su estado y uno porque tenía antecedentes de úlcera duodenal. Otros ocho casos presentaron el cuadro de infarto en el ECG antes de que se pudieran tratar con anticoagulantes o se hubiesen dado en dosis suficiente Hubo cinco muertes (28 por ciento) en este grupo.

3. La mayoría de los 200 casos aproximadamente se hospitalizaron y se les dió tratamiento anticoagulante. Cuatro de ellos presentaron el cuadro de infarto del miocardio en el ECG. Dos (50 por ciento) de estos cuatro, murieron.

4. Una extensión de la lesión miocárdica puede presentarse a pesar de los anticoagulantes; pero es nuestra impresión que esto ocurrió en nuestros enfermos mas a menudo cuando los anticoagulantes se interrumpieron o no se dieron a dosis suficientes.

5. No es posible predecir la evolución de los enfermos que han sufrido la oclusión coronaria aguda y en quienes los ECGs pueden presentar o no el cuadro típico del infarto.

ZUSAMMENFASSUNG

1. Während der vergangenen 5 Jahre wurden ungefähr 200 Fälle beobachtet, deren klinische Vorgeschichte den starken Verdacht eines Herzinfarktes erweckte; jedoch zeigte das Elektrokardiogramm lediglich Veränderungen T-Zacke und in wenigen Fällen außer diesen Veränderungen geringere Abweichungen der RS-T-Strecke. Bei 22 von diesen Patienten schloß sich nach einem Intervall von einem Tag bis zu mehreren Wochen an den ersten Schmerzanfall eine zweite Attacke an mit Entwicklung der typischen Infarkt-Zeichen im Elektrokardiogramm.

2. 10 der Kranken wurden nicht mit Anticoagulantien behandelt 7 wegen Verweigerung des Krankenhausaufenthaltes, 2 weil ihr Krankheitszustand nicht für genügend schwer gehalten wurde und einer wegen eines Duodenalgeschwüres in der Vorgeschichte. Bei 8 weiteren Fällen entwickelten sich die elektrokardiografischen Infarktzeichen, ehe mit Anticoagulantien begonnen oder sie in genügenden Mengen gegeben werden konnten. In dieser Gruppe gab es 5 Todesfälle (28%).

3. Die Mehrzahl der etwa 200 Fälle wurden stationär behandelt und erhielt Anticoagulantien. Bei 4 von ihnen traten elektrokardiografische Zeichen eines Herzinfarktes auf. 2 (50%) von diesen verstarben.

4. Es kann zu einer Ausbreitung der Herzmuskelveränderung kommen trotz Anticoagulantien; aber nach unserem Eindruck geeschah dies an unserem Krankengut am häufigsten, wenn mit Anticoagulantien zurückgehalten wurden oder sie in nicht genügender Menge gegeben worden waren.

5. Es war nicht möglich, das weitere Schnicksal von Patienten genauer voraus zu bestimmen, die an einem akuten Coronarverschluß erkrankt waren und deren Elektrokardiogramme die typischen Anzeichen eines Infarktes aufwiesen oder auch vermissen liessen.

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A Double-Blind Study of Reserpine in Angina Pectoris*

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The many varied agents[12] suggested for the treatment of angina pectoris suggest the inefficacy of available drug therapy and indicate the need for more effective medication. Twelve reports[1,3-5,10,11,13,14,19,20,25,26] are available in which the rauwolfia group of drugs has been employed in this condition. The importance of the double-blind technique of drug evaluation in general[29,30] and in angina pectoris[2,4] in particular has been stressed. Inasmuch as only two such studies[4,13] are available, the following experience with reserpine† in angina pectoris is reported.

Methods and Materials

For the purposes of this study, angina pectoris is defined as anterior thoracic or substernal pain, pressure or discomfort with or without radiation, precipitated by effort and relieved promptly by rest or sublingual nitroglycerine. Patients satisfying these criteria were referred from various clinics of the Out-Patient Department of the Kings County Hospital Center†† to the Special Cardiac Clinic (Service B) for the double-blind investigation of reserpine.

At the first visit a complete history, with particular attention to exercise tolerance and nitroglycerine requirement, as well as a physical examination, was obtained from each patient. The following laboratory studies were obtained within one week: chest roentgenogram, electrocardiogram, ballistocardiogram (3-plane), fasting blood sugar, urea nitrogen and cholesterol. Medication was dispensed as reserpine, 0.1 milligram, or an identical placebo in identical envelopes containing a two or

TABLE 1—INITIAL HISTORY

Characteristic	Placebo 18 Cases	Reserpine 18 Cases
Males - Females	9.9	7.11
White - Non-white	13.5	11.7
Average age	60.8	60.7
Average duration of angina	3 yrs.	2.8 yrs.
Myocardial infarction	7	8
Hypertension	4	6
Diabetes	3	4
Left sided failure	3	6
Average daily TNT* requirement	2.5	2.4
Average maximum exercise tolerance	7 blocks	4.3 blocks

*Nitroglycerine tablets

*From the Department of Medicine, State University of New York, Downstate Medical Center, and Special Cardiac Clinic (Service B), Out-Patient Department, Kings County Hospital Center.
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†Kindly supplied by Ciba Pharmaceutical Products, Inc., courtesy of Dr. F. J. Vinci.
††The authors[15,24] previously reported their experience with acute myocardial infarction in a similar group of patients in this Institution.

TABLE 2—INITIAL PHYSICAL FINDINGS

Characteristics	Placebo 18 Cases	Reserpine 18 Cases
Range of weight	102 - 179¾	104¼ - 178
Average weight	152.6	147.4
Range of blood pressure	110/60 - 210/100	110/62 - 195/100
Average blood pressure	149/80	151/84
Pulmonary congestion	2	1
Cardiomegaly	1	2
Hydrothorax	0	1
Ankle edema	0	1
Range of pulse	60 - 100	60 - 96
Average pulse	77	79

three weeks' supply, to be taken after meals and at bedtime. Patients were seen at two or three week intervals, at which time the average daily nitroglycerin requirement, maximum exercise tolerance and possible side effects were noted. The recording of these data was done by the patient at home on a daily report card, modified after that of Greiner *et al.*[6] (Fig. 1). During each follow-up visit, blood pressure, pulse, cardiopulmonary and peripheral vascular examination was performed. At the end of six months of therapy, the initial clinical and laboratory examinations were also repeated. Those patients who received the placebo were transferred to reserpine, and vice versa, with the exception of five patients who received only one mode of therapy. In every instance, they were told simply that the drug being supplied was to ameliorate their angina, but that an immediate effect would not be observed. The patients were usually seen by the same examiner throughout the course of treatment, and in no instance were they made aware of the research nature of the project.

The degree of improvement in the present report is simply stated as *improved* or *not improved* according to the presence or absence of better than 50 per cent decrease in the average daily nitroglycerine requirement or better than 50 per cent increase in the maximum exercise tolerance. The recording of lesser degrees of improvement was deemed

DAILY REPORT CARD

Patient: ..... O.P.D. No.: .....

BRING THIS CARD TO CLINIC NEXT VISIT.

Day of Week	How much pain in the heart did you have each day?					
	SAME HEART PAIN AS USUAL	LESS HEART PAIN THAN USUAL - GOOD DAY	MORE HEART PAIN THAN USUAL - BAD DAY	NO HEART PAIN AT ALL	NO. OF NITROGLYCERIN TABLETS	OTHER COMPLAINTS
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						

Before going to bed each night, check (✓) the space that describes your heart pain for the entire day.

FIGURE 1

TABLE 3—INITIAL ABNORMAL LABORATORY DATA

	Placebo	Reserpine
True fasting blood sugar (mg. per cent)	14 cases	13 cases
101 - 129	3	4
130 and over	2	3
Blood urea nitrogen (mg. per cent)	13 cases	12 cases
25 - 50	6	6
Serum cholesterol	13 cases	12 cases
251 - 350	7	8
351 and over	4	1
Cardio-thoracic ratio	13 cases	14 cases
over 50 per cent	8	8
Electrocardiogram	18 cases	17 cases
Old infarction	5	5
Left ventricular hypertrophy/strain	5	4
Non-specific ST - T changes	5	6
Left bundle branch block	—	1
Right bundle branch block	1	2

unwise because of the relatively small number of cases, the spontaneous variations in the syndrome of angina pectoris, and the relatively crude criteria of improvement.[7]

Observations

Tables 1, 2 and 3 delineate the initial clinical characteristics, physical findings and laboratory results in the two study groups. No important change in the above was evident during the course of observation and treatment with the exception of nitroglycerine requirement, exercise tolerance, blood pressure and pulse, all of which are discussed subsequently. Side effects were apparent in more than one-fourth of the patients.

Although the *nitroglycerine requirements* were decreased in several observation periods during reserpine administration, no over-all significant difference was noted between the placebo and reserpine study groups. This was also true of the 13 patients who received the drugs in sequence (Table 4).

Exercise tolerance data were essentially the same as recorded for nitroglycerine requirements regarding individual observation periods and the drugs in sequence (Table 4).

TABLE 4—PERCENTAGE OF CASES IMPROVED

	Two Weeks		Four Weeks		10 Weeks		16 Weeks		Six Months		Total Study	
	TNT *Req.	Exer. **Toler.	TNT Req.	Exer. Toler.	TNT Req.	Exer. Toler.	TNT Req.	Exer. Toler.	TNT Req.	Exer. Toler.	TNT Req.	Exer. Toler.
All cases												
Placebo	66	10	44	40	44	25	22	28	44	42	42	27
Reserpine	56	25	45	34	27	33	48	44	58	28	45	35
Sequential cases†												
Placebo	60	0	28	25	38	0	25	17	33	33	35	15
Reserpine	44	25	33	20	33	67	50	42	50	28	37	35

Key: *Nitroglycerine Requirement
**Exercise Tolerance
†Patients Receiving Both Drugs Sequentially

TABLE 5—SIDE EFFECTS

Type	All Cases				Sequential Cases			
	Placebo (18) Number of		Reserpine (18) Number of		Placebo (13) Number of		Reserpine (13) Number of	
	Times	Cases	Times	Cases	Times	Cases	Times	Cases
Central nervous	15	11	22	13	6	6	16	11
Gastro-intestinal	9	5	2	2	6	4	2	2
Genito-urinary	6	3	—	—	4	2	—	—
Musculo-skeletal	9	5	2	2	7	4	2	2
Vasomotor	5	3	3	3	2	1	1	1
Totals	44	27	29	20	25	17	21	16
Per cent of patients	32		26		42		31	

A *decrease in blood pressure* of more than 20 mm. systolic and/or 10 mm. diastolic occurred in more than 60 per cent of both treatment groups. A slowing of the pulse was observed in 55 per cent of the placebo group and in 33 per cent of the reserpine group. *Weight loss* of more than three pounds was noted in about 20 per cent of both groups, whereas a *weight gain* of more than three pounds was detected in about 30 per cent of both groups.

Side effects were defined as symptoms appearing during the course of therapy that were not present at the outset. They were classified according to the following types: central nervous, gastro-intestinal, genito-urinary, musculo-skeletal, and vasomotor. There was no significant difference in the proportion of patients exhibiting side effects between the placebo (32 per cent) and the reserpine (26 per cent) groups. This was also true of the 13 patients who received the drugs in sequence (Table 5).

TABLE 6—SUMMARY OF REPORTED EXPERIENCE WITH RAUWOLFIA SERPENTINA IN ANGINA PECTORIS

Author	Preparation	Number of Patients	Type of Patient	Percentage of Patients Improved*	Comments
Agnoletto[1]	Adrenosine, Hydroquinidine and Reserpine	5	—	Less favorable than in Arrhythmias	No controls
Braun[3]	Reserpine or whole root	11	—	100	No controls
Deitz[4]	Alseroxylon ± PETN**	22	Private	77-100	Double-blind
Ford and Rochelle[5]	Rauwolfia Serpentina	14	V.A.	75	No controls of group of 44 hypertensives
Hilden et al[10]	Reserpine	—	Clinic	"Great Number"	No controls of group of 30 hypertensives
Hughes et al[11]	Reserpine	2	Clinic	50	Of group of 62 hypertensives
	Alseroxylon	10	Clinic	60	Of group of 43 hypertensives
Lewis et al[13]	Alseroxylon	15	—	93	Double-blind
Livesay et al[14]	Alseroxylon	16	Clinic	60	No controls of group of 43 hypertensives
Pieri et al[19]	Raubasine	55	—	"Encouraging"	No controls
Plotz[20]	TNT, PETN and Reserpine	100	Private	93	Placebos for one week
Snow[23]	PETN and Alseroxylon	25	Private	Most to 100	No controls
Szajna[26]	Reserpine ± Heparine and Phenobarbital	10	—	100	No controls

*TNT Requirement/Exercise Tolerance **Pentaerythritol tetranitrate

TABLE 7—FREQUENCY (PER CENT) OF SIDE EFFECTS WITH RESERPINE

			Rosenberg and Malach	
Number in Series	Hughes[11] 62	Winsor[23] 65	Reserpine* 13	Placebo* 13
Nasal Stuffiness	70	21.3	—	—
Increased Appetite	30	—	—	—
Weight Gain	49	22.4	31	16
Fatigue and Weakness	49	—	23	—
	28	30.	16	—
Diarrhea	6	8.5	—	—
Dizziness	6	—	16	—
Aching Legs	—	12.	16	16

*Identical patients

A significant difference, however, was noted between the two groups in the occurrence of dizziness, as an individual symptom, which was reported once among the 18 patients receiving the placebo, and eight times among the 18 receiving the reserpine ($P<0.01$).

Discussion

On theoretical grounds, reserpine and other rauwolfia alkaloids might be expected to be of benefit in angina pectoris. According to most workers[14,18,21,27] these drugs act centrally at the levels of the hypothalamus by partially suppressing the sympathetic predominance over parasympathetic function. Some inhibition to central vagal stimulation by blockade of afferent impulses has also been noted.[14] For a drug like reserpine to be effective in angina pectoris, a favorable relationship between the coronary circulation and myocardial demands must be effected. The following known actions of reserpine might be expected to achieve this purpose: (1) that of a tranquilizer or sedative, (2) that of a mild hypotensive agent, (3) that of a bradycrotic drug, and (4) that of counteracting the oxygen-wasting properties of catecholamines in the heart muscle.[3,22]

The reported experience with the rauwolfia drugs in angina pectoris is not abundant. There are 12 reports in the available literature between 1954 and 1958, seven American and five European. In eight series[1,3,4,13,19,20,25,26] the drug was employed primarily in angina pectoris, while in four[5,10,11,14] it was used specifically in hypertension, and observations were made as to the effect on angina. Only two studies[4,12] were of the double-blind variety. As detailed in Table 6, 60 to 100 per cent of patients in the various series demonstrated subjective improvement in the form of increased exercise tolerance or decreased nitroglycerine requirement or both. In our series, 45 per cent evidenced improvement in one or both of these respects.

Failure of reserpine in divided doses as compared to a placebo to affect angina pectoris favorably in our patients may be explained as follows. Very few double-blind controlled studies have been reported in the literature. Whereas reserpine might be expected to favorably influence angina in the hypertensive patient with angina, in our experience the average blood pressure and pulse of the group were within normal limits initially and during the course of therapy. The duration of therapy in previously reported series would appear to be inadequate (two to eight weeks), perhaps with the exception of the study of Braun[3] and those instances where the rauwolfia was administered primarily to hypertensive patients. In our study reserpine was given for six months.

Likewise, our experience once again reaffirms the ability of placebos to produce side effects, as has been demonstrated amply in the past.[30] Thus, when considered according to the type of side effect, e.g. central nervous system, there was no significant difference in our series between the group receiving the placebo and that receiving the reserpine. The difference between the incidence of the individual symptom of dizziness in our two groups of patients is significant, however, there being a positive correlation with reserpine administration, but no correlation with hypotension. In the only two reported double-blind studies with rauwolfia in angina pectoris, no data are given as to the occurrence of side effects. Comparison of our experience with that in the literature dealing with the treatment of hypertension with reserpine is presented in Table 7. In the present report there was a notable absence of untoward effects such as nasal stuffiness, increased appetite, and diarrhea and a lower incidence of weight gain, fatigue, and sedation. The occurrence of weight gain and aching legs in our placebo group again argues for the necessity of the double-blind technique in drug evaluation.

SUMMARY

1. A double-blind study of reserpine (0.4 mg. per day) and placebo for angina pectoris in 18 city hospital out-patients is presented. Thirteen patients received both drugs in sequence.

2. The two groups of patients were similar in clinical and laboratory findings.

3. No significant difference in improvement of exercise tolerance, nitroglycerine requirement or both was observed between the two groups.

4. The failure of reserpine to be beneficial in angina pectoris in our series may be attributed to the low incidence of hypertension, the long duration of therapy, and the apparent inefficacy of this agent.

5. The difference in side effects was negligible, except for dizziness which was significantly more frequent in the reserpine group.

ACKNOWLEDGEMENTS: Grateful acknowledgement is given to Miss Irene Cambridge and the staff of the Kings County Hospital Record Room, Mrs. Martha Goldman and the staff of the I.B.M. Service Center, and to Mrs. Pauline Edelson, Mrs. Jeanette Magarello, Mrs. Mary Schwartz and Miss Helen Pomerantz for technical assistance.

RESUMÉ

1. Une étude par le procédé du "double-blind" porte sur l'action de la reserpine (0.4 mg. par jour) et d'un placebo dans l'angine de poitrine chez 18 malades consultants d'un hopital municipal. Treize malades ont reçu les deux traitements l'un à la suite de l'autre.

2. Les résultats des examens cliniques et de laboratoire étaient les mêmes dans les deux groupes de malades.

3. Il n'a pas été observé de différence significative entre les 2 groupes, en ce qui concerne l'amélioration de la tolérance a l'effort, la nécessité d'utiliser la nitroglycérine, ou l'une et l'autre.

4. Les raisons de l'échec de la reserpine dans le traitement de l'angine de poitrine peuvent être les suivantes: le faible pourcentage d'hypertendus, la longue durée du traitement, et l'inefficacité apparente de ce médicament.

5. La différence dans les effets secondaires a été négligeable, sauf pour la tendance vertigineuse qui a été plus fréquente de façon significative dans le groupe traité à la reserpine.

RESUMEN

1. Se presentan los resultados de un estudio por el método doble-ciego usando reserpine (0.4 miligrs por día) y placebo para la angina pectoris llevado a cabo en 18 hospitales de la ciudad en servicio de externos. Trece enfermos recibieron ambos productos en sucesión.

2. Los dos grupos fueron similares en hallazgos clínicos y de laboratorio.

3. No se observó diferencia de importancia en los dos grupos en cuanto a mejoría de la tolerancia al ejercicio, requerimiento de nitroglicerina, o ambas cosas.

4. La falta de efecto benéfico de la reserpina en angina de pecho en nuestra serie puede atribuirse a la baja frecuencia de la hipertensión, la larga duración del tratamiento y la aparente ineficacia de este medicamento.

5. La diferencia en efectos colaterales fue desdeñable, excepto para el mareo que fue más frecuente de manera significante en el grupo de la reserpina.

ZUSAMMENFASSUNG

1. Bericht über einen doppelten Blindversuch mit Reserpin (0.4 mg pro Tag) und Placebo wegen Angina pectoris bei 18 ambulanten Patienten des Stadtkrankenhauses. 13 Kranke erhielten beide Mittel nacheinander.

2. Beide Patientengruppen waren einander in ihren klinischen und Laboratoriumsbefunden ähnlich.

3. Es wurde keine entscheidene Differenz hinsichtlich besserer Verträglichkeit der Belastung, Bedarf an Nitroglyzerin oder beiden zwischen den 2 Gruppen beobachtet.

4. Das Versagen des Reserpins als eines nützlichen Mittels für die Angina pectoris in unserem Krankengut kann man der geringen Häufigkeit einer Hypertension, der langen Dauer der Therapie und der augenscheinlichen Wirkungslosigkeit dieses Mittels zuschreiben.

5. Die Differenz der Nebenwirkungen war unbedeutend, abgesehen von Schwindel, der beträchtlich häusiger in der Reserppingruppe vorkam.

All references will appear in reprints.

A Bear by the Tail?
The Discontinuance of Anticoagulant Therapy

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The use of anticoagulants for the prevention and treatment of thromboembolic conditions is now generally accepted. For some conditions such as acute thrombophlebitis, the duration of treatment is usually short, ranging from three to five weeks. However, for many conditions a more prolonged course is indicated, and with the accumulation of greater experience and an aging population this list is lengthening. It now includes any recurrent thromboembolic state and any condition that is known to exhibit such tendencies. Among these are recurrent pulmonary emboli, from whatever source, and recurrent thrombophlebitis, myocardial infarction, rheumatic heart disease with embolization, auricular fibrillation, cerebral transient ischemic attacks, recurrent cerebral thromboses. The total number of patients who are candidates for long-term anticoagulant therapy is, therefore, large but not known. Some estimate can be arrived at when it is appreciated that over one million persons in the U. S. received anticoagulant therapy of some duration last year and a similar figure appears reasonable for Europe and the rest of the world. If an estimated ⅓ to ½ of these are logical candidates for long-term therapy, the medical profession is confronted with a problem for which we are neither adequately staffed nor equipped. There are technical, economic, transportation and social aspects of this situation that require careful planning without further delay.[1] They can be approached in several ways:

1. All medical students should be taught the fundamental concepts of coagulation and the basic principles of anticoagulant therapy.

2. All clinical laboratory technicians should be trained to carry out accurately the most commonly used tests for the control of anticoagulant therapy.

3. Courses for older clinicians and technicians should be available.

4. The U. S. Public Health Service should establish geographically located centers to which clinicians and technicians can turn for advice and check for the accuracy of their procedures.

5. Simpler tests and those which permit the mailing in of blood specimens should be applied in the U. S. as they are in Norway.

6. Much more information must be developed which will help in the selection of the patients in whom this therapy may be discontinued with reasonable safety. This is one of the most important facets of our approach. We often do have "a bear by the tail," and we do not know when it is safe to let go.

*From Cornell University Medical College.

Studies[2,3] in our own clinic have convinced us of the danger of discontinuing anticoagulants when the patient has demonstrated the tendency to chronic or recurrent thromboembolism engrafted on an atherosclerotic or rheumatic heart, or a thrombophlebitic disease state. Keyes reported that one-half of his post-myocardial infarction patients who discontinued anticoagulation suffered new infarcts within from 5 days to 20 months, with a mortality of 50 per cent; Sise, Gauthier and Hecker[4] reviewed the records of 239 patients who had received long-term anticoagulation predominately for atherosclerotic cardiovascular disease. Thirty-three abruptly stopped anticoagulation because of hemorrhagic complication—11 of these developed thromboembolic complication within one day to three months—seven of these died. Thirty additional patients defaulted on the therapy—nine thromboembolic complications developed in this group of which six were fatal. This confirmed our experience reported by Carter,[3] as well as that of Owren,[6] Askey[7] and others. Similar tragedies have occurred when anticoagulants have been discontinued for surgery. One of our patients with rheumatic heart disease, auricular fibrillation and previous embolization, stopped taking dicumarol prior to a tooth extraction. This was delayed ten days, and in that interval she developed a cerebral embolus with a permanent hemiplegia. Others have had embolic complications. These experiences led us to study the possibilities of conducting oral surgery under adequate anticoagulant therapy. With proper surgical technic, this can be done with far less danger to the patient.[5] Other minor surgery is being carried out with the patient under good anticoagulant therapy. Indeed, even heart surgery has been conducted under these conditions by Storm[8] of Copenhagen and Miscall[9] of New York. This is technically more difficult and should only be considered under the most expert and favorable circumstances.

Under what conditions, then, are we justified in discontinuing anticoagulant therapy? We do not know in any given case whether a thromboembolic complication will arise. It has been suggested that this represents an excessive swing toward clotting or "rebound phenomenon," but the evidence, as determined by changes in the clotting mechanism, that this actually happens is not conclusive. It seems probable that this most commonly represents a return to the state the patient would have been in without the anticoagulant therapy, e.g. a "catching up" phenomenon. For example, his atherosclerosis has progressed, producing more narrowed arteries which are vulnerable to closure by clotting when the inhibition of the anticoagulation is removed. Nevertheless, common sense dictates that all of these patients should not be kept on anticoagulants for their remaining life span.

The following suggestions, therefore, are advanced as general guidelines. Anticoagulant therapy may be discontinued on a trial basis under the following conditions:

1. Acute thrombophlebitis after three to five weeks with complete disappearance of signs of the acute process.

2. Pulmonary embolism after three months of freedom from recurrence, except when the source has been a fibrillating heart which has continued to fibrillate.

3. Myocardial infarction after a first mild infarction—at the end of one year with minimal or no symptoms.

4. Retinal vein or artery thrombosis after three months without additional thromboembolic complications.

5. After a prophylactic course following surgery for two to three weeks with no complication.

6. Conversion of a fibrillating heart to normal rhythm—after three months of freedom from further disturbances in rhythm or embolic phenomena.

In each case, the anticoagulant should be tapered off over a two to three week period; generally, the possible risks should be discussed with the family—and the patient, if he is suitably oriented.

It is recognized that these are arbitrary time limits which should not be adhered to when any contraindications arise.

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PULMONARY INFARCTION IN DISORDERS ASSOCIATED WITH THE SICKLE CELL TRAIT

Sickling of red cells was demonstrated in three patients with pulmonary infarction. Studies of their abnormal hemoglobin showed their relevant genetic constitutions to be heterozygous. The second and third patients had the sickle cell trait alone; the first patient had this trait combined with that for abnormal hemoglobin C (hemoglobin S-C disease). These findings do not prove that the illnesses from which the patients suffered were a consequence of intravascular sickling, but no other cause for pulmonary infarction in these previously healthy ambulant men could be found and there was collateral evidence of activity of the sickling process.

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ELECTROCARDIOGRAM OF THE MONTH

Edited by Stephen R. Elek, M.D.

Cardiac Amyloidosis: Electrocardiographic Changes Simulating Ischemic Heart Disease

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A 53 year-old office manager came to the Mayo Clinic on June 22, 1955, because of easy fatigability that had appeared insidiously during the preceding six months. This symptom was most prominent toward mid-afternoon and evening. He gave no history of anginal pain, dyspnea or heart disease. The principal cardiac finding on examination was a grade 2 systolic murmur of "musical" quality maximal at the apex and transmitted toward the right second intercostal space.

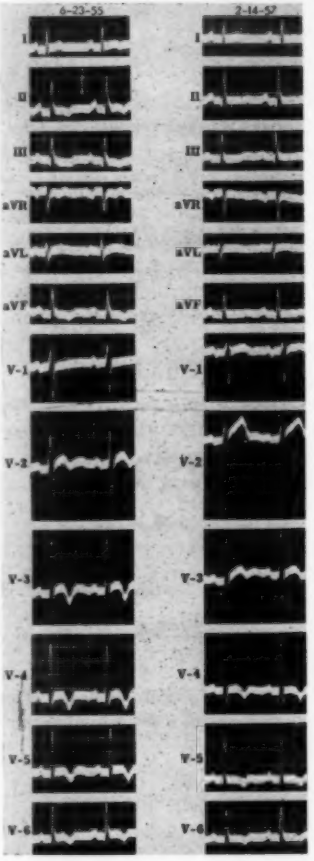

FIGURE 1: Electrocardiograms made on admission and approximately 20 months later.

X-ray examination revealed no cardiac enlargement. An electrocardiogram taken on June 23, 1955 (Fig. 1) showed repolarization abnormalities and T-wave changes considered consequent to a recent myocardial infarction; he was, therefore, hospitalized. Serial electrocardiograms showed stabilization of the pattern without the usual expected resolution. Ischemic heart disease was suspected and, in addition, the possibility of ruptured chordae tendineae was thought to account for the apical systolic murmur.

He was re-examined frequently during the next two years, during which the cardiac findings remained essentially unchanged (Fig. 1). However, he had increasing fatigability along with anorexia, loss of 20 pounds, and increasing hepatic enlargement. Subcostal needle biopsy of the liver disclosed amyloid infiltration.

The subsequent course was characterized by exertional dyspnea, increasing weakness peripheral edema of the lower extremities and abdominal ascites. These manifestations of congestive heart failure became refractory to the usual decongestive measures. On May 18, 1958, the day

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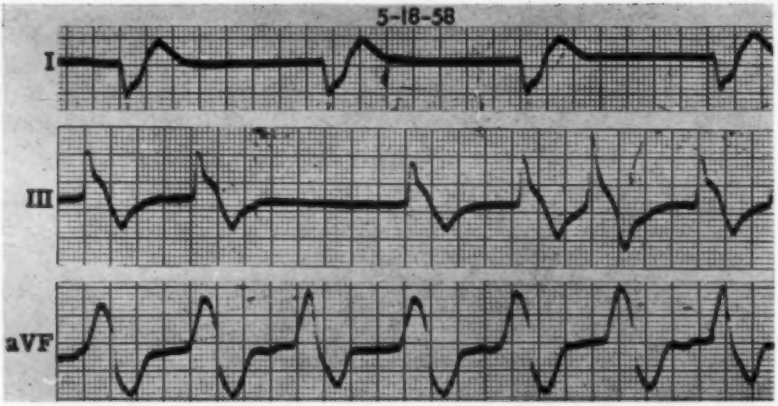

FIGURE 2: Electrocardiogram made the day before death.

preceding his death, cardiac irregularity was noted and the electrocardiogram showed complete atrioventricular dissociation (Fig. 2) with bizarre and widened QRS complexes reflecting aberrant intraventricular conduction.

At necropsy, the presence of systemic amyloidosis involving the heart, liver, skin and gastrointestinal tract was confirmed. Deposits of amyloid were found in the walls of vessels within the myocardium of the ventricles and right atrium. In addition, the mitral valve leaflets were infiltrated with amyloid, which presumably explained the origin of the systolic murmur. Only slight to moderate coronary sclerosis was present, and no myocardial infarction or epicardial necrosis was found.

In retrospect, a noncoronary cardiac myopathy, such as amyloidosis, could be surmised from the absence of anginal pain throughout his clinical course in concert with the manifestations of congestive failure and persistent electrocardiographic changes simulating those of myocardial ischemia.

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We should also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

Combined Salicylate, Corticotropin and Corticosteroid Therapy in Acute Monocyclic Rheumatic Pancarditis

A Preliminary Report*,†

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The first published accounts of the effects of corticosteroid and corticotropin on acute rheumatic carditis by Hench and co-workers in 1949-50[1,2] precipitated an enthusiastic clinical investigation of these hormones and their analoguese. An attitude of mounting optimism prevailed.[3-6]

In general, investigators concerned themselves with the relative merits and the toxic or untoward effects of various hormone regimens as opposed to salicylates, and related the disease response to the amount and duration of the medication administered.[7-14] The treatment failures were usually proportional to the time elapsed prior to treatment.

On this idyllic scene, the joint report of the "Cooperative Clinical Trial" (1955) cast a pall of disenchantment. In a study of 497 children with acute rheumatic fever, they concluded that neither cortisone nor corticotropin was superior to aspirin, either in terms of the response of the acute disease or of residual heart damage one year later.[9]

TABLE 1—DIAGNOSTIC STUDIES*

	Complete Blood Count									Sed. Rate				
Date	Hb.	RBC	WBC	Polys.	Stab.	Lymph.	Mono.	Eos.	Baso.	Uncorr.	Corr.	HCT	CRPA	ASOT Todd U.
1/18	11.3	2.95	11500	78	3	19				60	40	33	4+	125
1/26										15	14	41	1+	166
2/1										3	3	42		
2/4													0	250
3/8	12.45	3.98	6000	57	1	32	9	1		3	3	42	0	50
4/5										5	3	40		
5/3	12.15	4.27	7350	57		36	4	3		7	7	42		
6/7	12.15	4.1	6750	59	1	31	4	4	1	5	3	40	0	50

*In addition, the laboratory studies on admission included:

1. Negative urinalysis.
2. Negative V.D.R.L.
3. Normal blood glucose (122 mg. per cent 2 hours postabsorptive).
4. Negative PPD (No reaction to *intermediate strength*, 0.0002 mg. at 48 hrs.).
5. Negative L-E Preparation.
6. Positive throat culture for Alpha hemolytic strep.+++, Staph. albus+, N. catarrhalis+ (virulence not determined).
7. Negative blood culture (no growth 2/1/60).
8. Absolute eosinophile count 56/mm³, prior to therapy.

For an explanation of this material see section of text under Diagnostic Investigation.

*Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.
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This authoritative dissension created a tide of pessimism and in its wake, an explanation of this enigma was sought vociferously. One investigator postulated that rheumatic disease may vary from one section of the country to another.[15] This thesis, however, could hardly be expected to mollify the unsettled climate of opinion within the confines of a given geographic area.

In summing up the "Current Status of Therapy in Rheumatic Fever" one year ago, the Council on Drugs of the American Medical Association made the following comments:[13]

> "With the advent of cortisone . . . hope was high that at last an agent was available which would suppress rheumatic inflammation . . . However, nine years after the introduction of corticosteroid therapy . . . it still cannot be stated . . . whether these agents are of value in carditis or, indeed, whether they may not actually be harmful."

The question of the superiority of one form of steroid regimen or another as opposed to salicylates has long held the fascination of investigators and will probably never be resolved to everyone's satisfaction. Nevertheless, it is generally agreed each of these will suppress the manifestations of acute rheumatic fever[1-13,16-18] and, although both corticotropin and aspirin have been employed during the withdrawal period of corticosteroids,[7,16] it remains to be seen whether their effect might be additive when administered simultaneously.

We are reporting the effect of the concomitant administration of corticotropin, corticosteroids and salicylates in a patient with acute

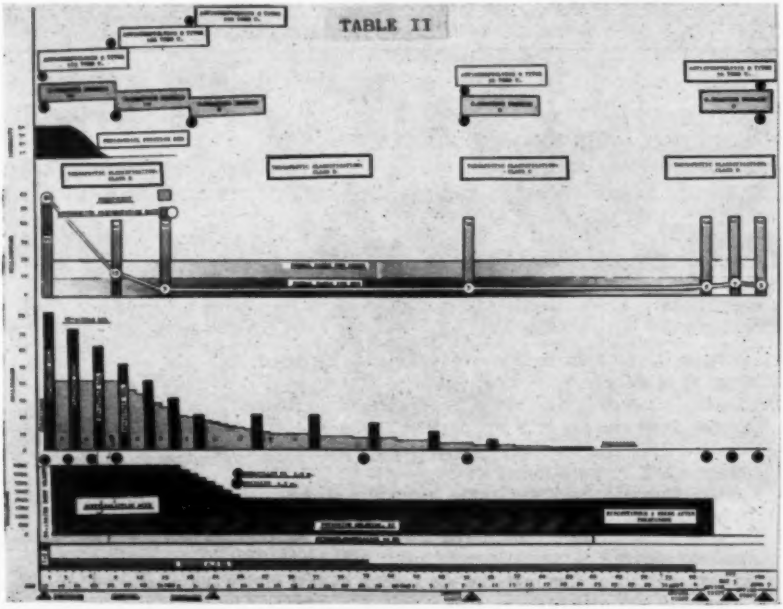


TABLE 2: The relationship of the administration of aspirin, prednisone and corticotropin gel, as well as penicillin and other medication, to disease response as reflected in a disappearance of the pericardial friction rub and a return to normal of the acute phase reactants is illustrated in a composite graph. For an explanation of this material see sections of text under Medication and Hospital Course.

rheumatic pancarditis. The rarity of this entity in our semi-tropical climate interdicts a statistically significant treatment experience.[19,20]

Case Report

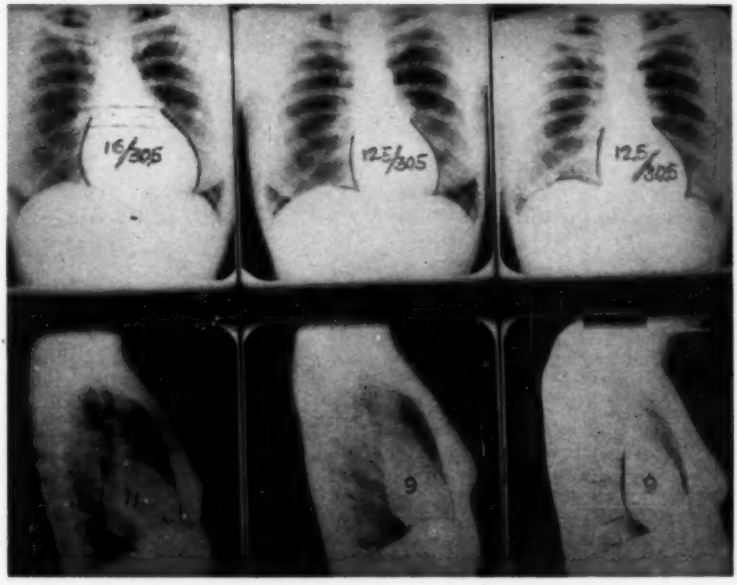
During the second week of an illness characterized by an abrupt onset of general malaise and rapidly developing prostration, a hectic fever with daily swings from 103° to 104°F. accompanied with drenching sweats, and sharp stabbing pains in the precordium and left shoulder, Mrs. D. L., a 53 year-old Cleveland housewife, was hospitalized on January 17, 1960.

She recalled that she had had a sore throat with an acute upper respiratory infection some two weeks before the onset. Upon arriving in Florida the second day of her illness, she summoned a physician who ordered her to bed and prescribed a broad spectrum antibiotic.** The fever continued and the chest pain failed to improve.

On the fourth day, a chest x-ray film was obtained. There was striking enlargement of the heart. Compared with a routine film a year before, the transverse diameter had increased from 13 cm. to 16.7 cm. An ECG on the same day showed elevation of RST-junctions and straightening of the proximal limb of the T-waves in all leads except AVR, compatible with acute diffuse myocardial or epicardial injury.

She remained in bed and medication was continued for an additional week without improvement. After conferring with her attending physician, arrangements were made for her transfer by ambulance (some 90 miles) for hospitalization.

Transfer was uneventful. On admission, she was feverish, pale and obviously ill. Her temperature was 101.6°F. (O), 102.4°F. (R), respiration 20, pulse 100 and regular and blood pressure 100/70. The heart was markedly enlarged, but there was no discrepancy between the outer left border of cardiac dullness and the apical thrust. A grade IV pericardial friction rub was of such intensity over the precordium that the first and second heart sounds were inaudible. There was a systolic and early diastolic intensification, but the rub was not transmitted. By exploring the chest, the first and second heart sounds could be heard in the left axilla and beneath the inner third of the clavicles bilaterally. Both the hepatojugular reflex and the Valsalva maneuver were negative. There was no cyanosis, neck vein distention, hepatomegaly, or dependent edema, and the lung fields were clear.



A B C

FIGURE 1: Chest roentgenograms in posterioanterior and left lateral views: (A) following admission; (B) after one week of treatment, and (C) four months later.

**PanAlba, Upjohn (tetracycline hydrochloride, 250 mg. and novobiocin sodium, 125 mg.) q.i.d.

A review of the past history and system inventory were essentially noncontributory. She said she had been told several years ago she had "a little murmur," but that "it was nothing serious."

In summary, the physical findings on admission were in keeping with a fibrinous pericarditis, with little or no serous component, and a pancarditis with diffuse cardiac dilatation.

Diagnostic Investigation

On the following day, the laboratory studies detailed in Table 1 were performed. The staff radiologist made a careful fluoroscopic inspection of the cardiac silhouette in multiple views with barium-filled esophagus both in the upright and recumbent positions. The following is abstracted from his interpretation: "The cardiac silhouette showed generalized enlargement . . . There was no specific chamber enlargement, although the left ventricle appeared to be predominant. A spot view was taken in the posteroanterior position both supine and upright. There was no noticeable change in the cardiac silhouette. The appearance does not suggest pericardial effusion."

Medication

Prophylactic: Although she had received a broad spectrum antibiotic for ten days prior to admission, one million units Duracillin FA, Lilly* were administered at 72-hour intervals for a total of three injections. On the ninth day, 1.2 million units of benzathine penicillin-G were administered in a single injection and at 30-day intervals thereafter.

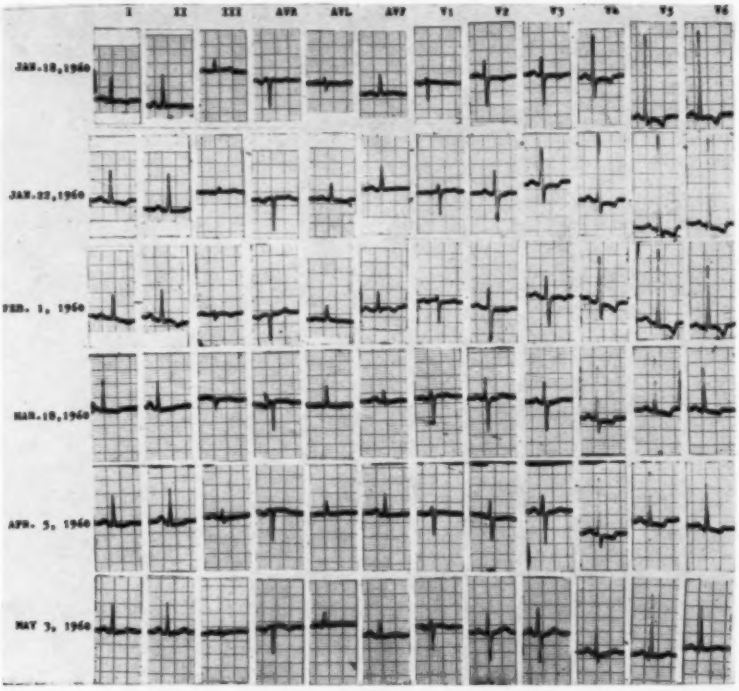


FIGURE 2: Serial electrocardiograms show the evolving pattern (waxing and waning) of an acute diffuse myocardial and epicardial injury. The T-wave inversion was progressive (February 1, 1960) in spite of a complete reversal of the acute phase reactants, restoration of normal heart size and the disappearance of pericardial friction rub. The pattern eventually returned to normal by the fifteenth week after treatment was begun. (The ECG, one week prior to admission, showing RST-J elevation, straightening of the proximal limb and increased amplitude of the T-waves, was not available for reproduction.)

*Duracillin FA, Lilly (750,000 U. crystalline procaine penicillin-G and 250,000 U. buffered penicillin-G, crystalline-sodium).

Antiphlogistic: Beginning the same day (January 18, 1960), an initial injection of 80 U. HP*ACTHAR Gel, Armour (repository corticotropin in 16 per cent gelatin) was given. Subsequently, the injections were made at 72-hour intervals with a reduction of 10 U. each injection. When the dosage had reached 20 U., the injections were continued at weekly intervals for two additional weeks and the dosage was then reduced by 5 U. each week. The final injection was given during the eighth week.

Prednisone was administered concomitantly by the oral route at six-hour intervals totaling 40 mg. per day, and was maintained at this level for nine days. On the tenth day, prednisone was reduced by 2.5 mg.; and, daily thereafter on alternate doses until the total amount administered reached 20 mg. per day. At this juncture, only 1 mg. was omitted each succeeding day and by the end of four weeks the total dosage had been reduced to 2 mg. q.i.d. Medication was then reduced by a single mg. every five days. Therapy was eventually terminated after nine weeks.

In addition, 80 gr. of enteric coated aspirin were administered in divided doses daily. After two and one-half weeks this was reduced by 5 gr. daily until a level of 40 gr. was attained, which was maintained until two weeks after prednisone therapy had terminated.

Supportive: Although there was no evidence of frank congestive failure, it was felt that the persistent tachycardia and generalized cardiac enlargement portended a failing myocardium for which digitalization was justified. Digoxin was administered orally in a single dose of 1.5 mg. and was maintained at 0.5 mg. daily, later reduced to 0.25 mg. and eventually interrupted at the end of the 11th week.

To avoid sodium and water retention, 50 mg. of hydrochlorothiazide were given at breakfast daily, and to obviate potassium depletion, 1.2 gm. of potassium chloride (enteric coated) were also given daily. Both were continued throughout steroid administration, but were interrupted when the latter was discontinued.

Hospital Course

The therapeutic response was dramatic. The temperature and pulse rate returned to normal within 24 hours and remained so throughout the hospital stay.

The intensity of the friction rub began to diminish by the third day and at the end of one week was no longer audible (Table 2). After the disappearance of the friction rub, the heart tones were essentially normal except for an evanescent grade I systolic apical murmur.

A recheck of cardiac size on the fourth day of therapy revealed a striking reduction of the transverse diameter of the heart to 13.8 cm. After one week of treatment, the cardiac size and contours were well within normal limits, the transverse diameter measuring 12.5 cm. (Fig. 1). The sedimentation rate had fallen from 60 mm./1 hour to 14 mm./1 hour and the hematocrit had increased from 33 vol. per cent to 41 vol.

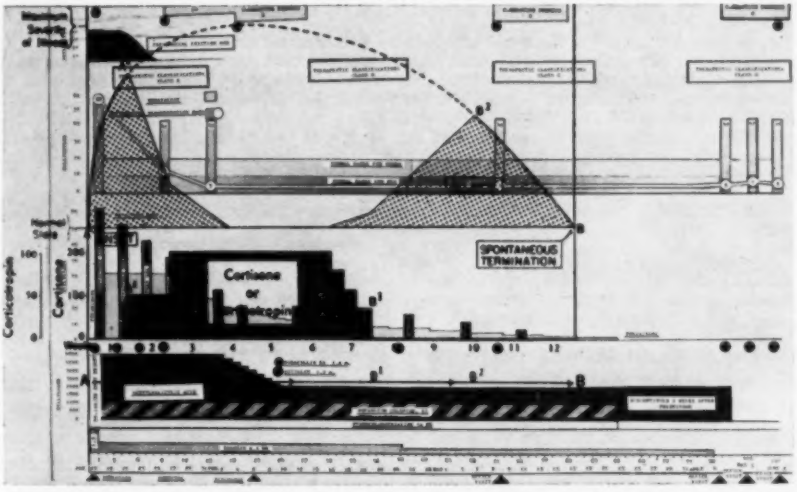


FIGURE 3: A theoretical and schematic representation of the effect of the short term administration of adrenocortical hormones on the clinical course of a monocyclic attack of rheumatic fever, demonstrating escape or relapse, is overlaid on Table 2. By the prolonged administration and gradual withdrawal of both hormones and aspirin, the regimen depicted in Table 2 minimizes the escape potential. (Overlay from Banim, J. J.: "The Effects of Cortisone and ACTH on Rheumatic Diseases," *Bull. New York Acid. Med.*, 27:75, 1951)

per cent. The CRPA fell from 4+ to 1+, but the ASOT had increased from 125 to 166 Todd U. (Tables 1 and 2).

At the conclusion of the second week of therapy (February 1, 1960) the sedimentation rate was 3 mm./1 hour and the hematocrit 42 vol. per cent. Three days later a recheck of the CRPA was negative and the ASOT had increased to 250 Todd U. (Tables 1 and 2).

There were no untoward reactions to the medication. At no time were there any manifestations of hyperadrenocorticoism, salicylate intoxication, sodium or water retention or potassium depletion. There was a gradual gain of weight of about one pound per week after the second week of therapy, which was attributed to improved nutrition.†

At the time of discharge, three weeks following admission to the hospital, the only abnormalities persisting were an elevated ASOT and an abnormal ECG pattern.

She was instructed to remain in bed for the first two weeks of convalescence at home (*therapeutic class E*), but after this, physical activities could be increased gradually at the direction of her attending physician. A therapeutic protocol (Table 2) was provided with the understanding that it was intended only as a guide, based on the assumption that her course would continue uneventful, which, happily was the case.

At the conclusion of two weeks at home, she progressed to *therapeutic class D* and in another two weeks, to *therapeutic class C*. For the next three months, she was given a free range of activity within *therapeutic class B*. She was then progressed to *therapeutic class A*.

Throughout convalescence, the sedimentation rate, hematocrit, CBC and CRPA have remained consistently normal. The ASOT, however, has never gone below 50 Todd U. The ECG pattern returned to normal 15 weeks after treatment was begun and has remained normal (Fig. 2). At the time of this report, our period of observations has been limited to six months.

CONCLUSION

1. The relative merits of aspirin, corticotropin and corticosteroids in the acute phase of rheumatic carditis has been the subject of numerous reports over the past decade, but the supremacy of any of these agents in terms of disease response has not been established.

2. It is generally agreed that any one of these agents, if administered in sufficient dosage, will suppress the manifestations of the inflammatory process of acute rheumatic fever.

3. It is postulated that a combination of these agents may have additive therapeutic value; hence, suppression of acute rheumatic activity may be accomplished with an appreciably smaller dosage of each with a consequent reduction of both toxic and untoward reactions.

4. A case of acute monocyclic rheumatic pancarditis successfully treated by the simultaneous administration of salicylates, corticotropin and corticosteroids is presented. It is believed this concept bears further exploration; however, no claim of originality is made for the treatment presented, nor is there the slightest intent to perpetuate a specific protocol.

5. Viewed in the light of our present knowledge of the natural course of rheumatic disease, and the purely suppressive role ascribed to these drugs, the rationale of inflexible, high dosage, short-term therapeutic protocols is questioned (Fig. 3).

ADDENDUM: At the conclusion of one year's observation, there is no evidence of residual heart damage.

Complete reference list will appear in the reprints.

†Deladumone 2X, Squibb (testosterone enanthate 180 mg. and estradiol valerate 8 mg. per cc. dissolved in sesame oil) was administered intramuscularly concurrently with the Bicillin at 30 day intervals as a protein anabolic agent throughout the course of steroid therapy.

Joint Report of the United States and International Committees on Pathology and Microbiology*

AMERICAN COLLEGE OF CHEST PHYSICIANS

The agenda was confined principally to a discussion of atypical acid-fast bacilli which are found in lesions of tuberculosis in man. These forms, which have been given various designations, like atypical, anonymous, or unclassified bacilli, cause one of the principal problems in tuberculosis work at the present time. The various forms were considered primarily from the viewpoint of identification. It was conceded that the most useful test for separating typical human from other mycobacteria was the niacin test. Because the technique is rather objectionable due to the irritation from the tear gas (cyanogen bromide) used, a micro method (Tarshis, *Am. Rev. Resp. Dis.*, 1960) is preferred.

Supplementary methods include the following:

Peroxidase, neutral red, serpentine cord, and thioglycollate. Of these, thioglycollate is considered the best if growth is obtained, but as growth is so difficult to achieve, the test is not of much use. Resistance to PAS, one gamma per ml. and TB1, one gamma per ml. may also be used.

In connection with determination of the virulence of mycobacteria, both the catalase test and guinea pig inoculation were considered. Some members felt that the catalase test and guinea pig inoculation could distinguish between tubercle bacilli that were virulent for human beings and those that were not. Another point of view was that both of these tests involved biologic parameters that were themselves highly variable. The end point of the catalase test is too commonly vague and difficult to interpret, while some strains producing human pathology are negative or only slightly virulent for guinea pigs. Both catalase test and guinea pig test are of some value, however, in the study of atypical forms of mycobacteria. For example, a strong catalase test with a negative peroxidase test is significant while the guinea pig is useful for various skin tests when PPD preparations are being tested. Finally, it was felt that virulence could not be determined in the absolute sense. It could only be inferred from the clinical situation.

The next item was a question of the infectious origin of the Runyon groups I and II. These are the so-called photochromogens and scotochromogens. Because these forms were found consistently in patients with open tuberculosis, it was considered altogether likely that they originated in tuberculous lesions although the percentage was rather low for both. In most of the reports, especially in the U.S.A., the photochromogens range from 1 to 3 or 4 per cent. In Europe, percentages are somewhat lower. Scotochromogens vary from 1 to 7 per cent and are quite irregular in their appearance from one section of the world to another or from one institution to another.

It was recommended that the schema for identifying mycobacteria (a copy of which is appended to this report) be used as a working guide until such time as a better one may be evolved. There was realization of the fact that this technique is probably too complicated for nontuber-

*Adopted in Miami Beach, Florida, June, 1960 and Vienna, Austria, September, 1960.

culosis hospitals to employ and will be changing as new tests are evolved. The incidence of the tentative groups has not been established for different regions.

Of 1,000 consecutive specimens examined recently at the Missouri State Sanatorium, there were in

Group I	0.6%	Group IV	3.6%
Group II	5.6%	Typical T.B.	61.0%
Group III	29.2%	Total	100%

It was not deemed expedient or even possible at this time to offer a permanent classification of mycobacteria found in man any more than the following:

1. *M. tuberculosis*—human and bovine.
2. Mycobacteria with potential properties of virulence including most "atypicals," as well as *M. avium, M. leprae, M. ulcerans, M. balnei,* and *M. johnei.*
3. Pure saprophytes.

M. leucoflavin and *M. luteum* should not be considered as pathogenic for human beings.

Bogen of the United States reported on the variations in mycobacteria in various sections of the world, especially in Africa where there are three different varieties of acid-fast bacilli causing tuberculosis. One is the European variety with normal guinea pig virulence and the second, which he called the "Indian variety," with attenuated virulence for guinea pigs, and a third with a high virulence for guinea pigs which also shows a degree of virulence especially showing in the lungs of rabbits. These latter strains are to be designated as dysgonic human strains. In India, there are only two varieties found, the European type and the Indian type, the latter having a reduced virulence for guinea pigs. They also have a low peroxidase reaction, are catalase negative and INH resistant. The group IV strains are those that grow rapidly on regular media. They are chiefly nonpathogenic and are considered to be largely of saprophytic origin. Some are like the *M. fortuitum* exhibiting a peculiar virulence for animals, especially mice.

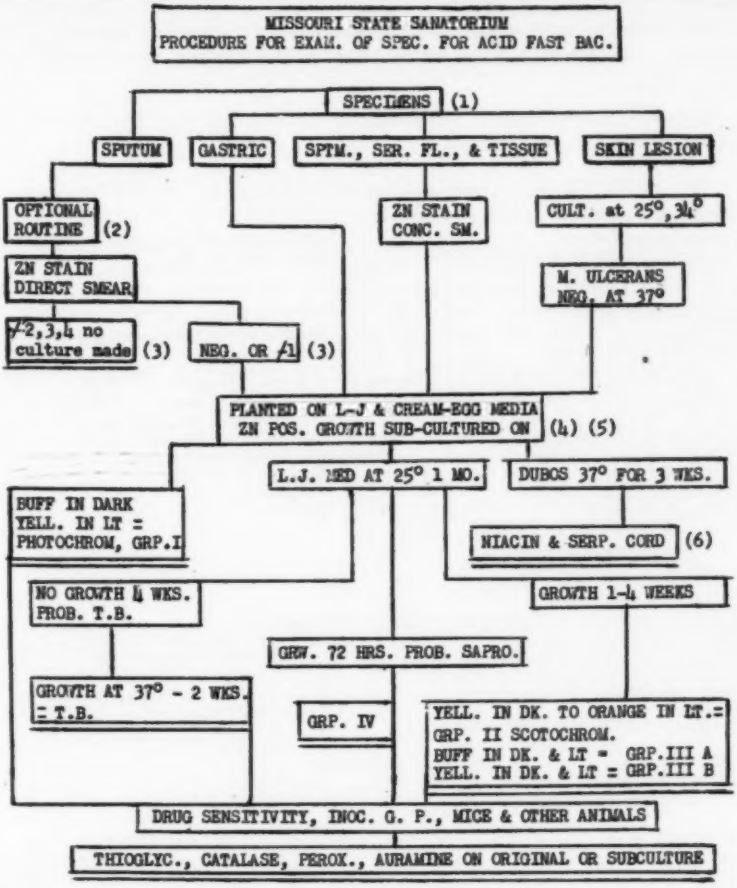
The next item considered was the possibility that the condition of the host may be responsible for certain of these atypical forms, especially the photochromogens and group III strains which have been reported in certain respiratory conditions as bronchitis, bronchiectasis, asthma, and emphysema. In children with lymph node involvement of the neck, there are occasionally found scotochromogens which may be due to a reduced resistance of the host.

The problem of mutation, or the role of mutation in the development of atypical strains, was discussed but there was no agreement as to the role that it plays in atypical forms of bacilli. Further investigation was recommended.

The next item on the agenda dealt with fungus infections of the lung, with special reference to aspergillosis. In England, the infection by Aspergillus is 100 per cent due to *Aspergillus fumigatus.* In Paris, the figure was given as 80 per cent with 20 per cent caused by other strains of Aspergillus. Most of the cases of Aspergillus infection were secondary to some other chronic disease of the lung. Some of these infections only

produce fungous tumors in the main bronchi with very little involvement of the pulmonary parenchyma. A small percentage actually invades the lung and produces a general involvement of the parenchymal tissue. Precipitin tests were recommended for establishing the presence of the disease, especially where it was necessary to separate the disease from allergic conditions. A double diffusion method in agar gel was also recommended.

Another consideration was the technique of cultivating fungi. It was recommended that the technique of the U. S. Public Health Service and the National Institute of Health in Bethesda, Maryland, be followed.


MISSOURI STATE SANATORIUM
PROCEDURE FOR EXAM. OF SPEC. FOR ACID FAST BAC.
SPECIMENS (1)
SPUTUM
GASTRIC
SPTM., SER. FL., & TISSUE
SKIN LESION
OPTIONAL ROUTINE (2)
ZN STAIN CONC. SM.
CULT. at 25°, 37°
ZN STAIN DIRECT SMEAR
M. ULCERANS NEG. AT 37°
#2,3,4 no culture made (3)
NEG. OR #1 (3)
PLANTED ON L-J & CREAM-EGG MEDIA ZN POS. GROWTH SUB-CULTURED ON (4) (5)
L.J. MED AT 25° 1 MO.
DUBOS 37° FOR 3 WKS.
BUFF IN DARK YELL. IN LT = PHOTOCHROM, GRP.I
NIACIN & SERP. CORD (6)
NO GROWTH 4 WKS. PROB. T.B.
GROWTH 1-4 WEEKS
GRW. 72 HRS. PROB. SAPRO.
GROWTH AT 37° - 2 WKS. = T.B.
GRP. IV
YELL. IN DK. TO ORANGE IN LT.= GRP. II SCOTOCHROM.
BUFF IN DK. & LT = GRP.III A
YELL. IN DK. & LT = GRP.III B
DRUG SENSITIVITY, INOC. G. P., MICE & OTHER ANIMALS
THIOGLYC., CATALASE, PEROX., AURAMINE ON ORIGINAL OR SUBCULTURE

1. ALL CONTAMINATED OR SUSP. CONT. SPEC. TR. 4% NACH.
2. ON KNOWN POSITIVE PATIENTS.
3. #1 = 3-10 ORG. PER SL; #2 = 1 - ORG. IN 2-3 FIELDS; #3 = 2-10 ORG. PER FIELD; #4 = 10 PER FIELD.
4. NO GROWTH AFTER 6 & 12 WEEKS, DISCARD AS NEGATIVE.
5. OVERGROWN WITH NON-A.F. BAC., FUNGI, ETC. - CONTAMINATED
6. TYPICAL T.B. IS NIACIN POS. AND USUALLY CORDED; ATYPICAL NIACIN NEGATIVE AND POOR OR NO CORDS.

Pesle of France recommended a "rolling" method of fluid media. Others recommended the addition of 0.5 mg. chloromycetin to the specimen bottle and a thorough cleaning of the mouth before collecting the sputum. All were in agreement that new and more sensitive methods must be found, not only for Aspergillus, but for many of the other yeast and mold infections. For obtaining various pathogenic yeast and molds from the soil, the method of the U. S. Public Health Service was recommended.

The problem of the staphylococcus infections in hospitals was considered only from the standpoint of the use of phage typing, especially of the tetracycline resistant staphylococci.

The last item on the agenda, animal parasites involving the lung, was only discussed in a limited manner. Especially important are the amebic abscesses, the Echinococcus cysts, and in the Orient, the *Paragonimus westermanni.*

A detailed classification submitted by Dr. William W. Coulter was accepted with minor modification and is as follows:

PULMONARY ANIMAL PARASITES

PROTOZOA

- Amoeba hystolytica
  - Found in sputum or pleural fluid
  - Complement fixation
- Plasmodia (Malaria) chiefly falciparum
- Toxoplasma gondii

NEMATHELMINTHES

- Nematoda
  - *Necator Americanus*
    - Larvae in sputum (rare) or stool
    - Eggs in stool
  - *Ancylostoma brasiliense*
  - *Toxocara canis*
  - *Ancylostoma canium*
  - *Uncinaria stenocephala*
    - Larvae (rhabditoid) in sputum
  - *Strongyloides stercoralis*
    - Eggs in stool
    - Adults in stool
    - Rarely eggs in sputum
    - More rarely adults in sputum
  - *Ascaris lumbricoides*
    - Eggs in stool
    - Larvae in stool (Larvae in sputum)
    - Adults in stool
  - *Trichinella spiralis*
    - Pulmonary infiltration
    - Eggs or larvae not found in sputum or stool
  - *Syngamus laryngeus*
    - Adults or eggs in sputum
  - *Wuchereria bancrofti*

PLATYHELMINTHES

- Cestoda
  - *Taenia echinococcus*
    - Intradermal test (Casoni)
    - Complement fixation (Weinberg)
    - X-ray appearance
    - History
    - Exploration and inspection of the cysts' contents
  - *Taenia solium*
    - Eggs in stool
    - Scolex or proglottids in stool
- Trematoma
  - *Paragonimus westermanni*
    - Eggs in sputum or stool
    - Complement Fixation
  - *Schistosomiasis mansoni, Japonicum and haematobium*
    - Ova in stools, rectal mucosa, or urine
- Mites
  - *Ascariasis*
    - Mites in sputum

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OXIDATIVE METABOLISM OF THE MYOCARDIUM MODIFIED BY NITROGLYCERIN: AN EXPERIMENTAL STUDY

Using a new technique for the measurement of coronary blood flow, essentially consisting of a right ventricle by-pass, myocardial oxygen metabolism has been studied in dogs both normal and previously treated by catecholamines. Nitroglycerin administered intravenously at a dose of 0.05-0.1 mg./kg., produces a temporary decrease of heart work, arterial blood pressure, coronary blood pressure, coronary blood flow and a temporary slight increase of heart rate and myocardial oxygen consumption. During perfusion of levarterenol, nitroglycerin produces a remarkable decrease of arterial blood pressure, heart work, coronary resistance, myocardial oxygen consumption, and a further increase of coronary blood flow, previously increased by catecholamines.

Marchetti, G., Maccari, M., and Merlo, L.: "Oxidative Metabolism of the Myocardium Modified by Nitroglycerin: An Experimental Study," *Atti, Accad Med. Lombardi*, 15:179, 1960.

CHRONIC CONSTRICTIVE PERICARDITIS

A paradoxical pulse, a dominant and sharp x descent in the jugular pulse, normal rhythm, more than slight enlargement of the heart shadow and persistent hydrothorax were noted more commonly in the group with active pericarditis than in those with chronic inactive pericarditis. Atrial fibrillation, a relatively small heart and pericardial calcification strongly indicated inactive cases of long duration. An early third heart sound and a characteristic electrocardiographic pattern occurred with equal frequency in both groups.

In differential diagnosis, perhaps the only serious difficulty is in distinguishing constrictive pericarditis from cardiomyopathy of clinically obscure origin. Factors indicating cardiomyopathy are a conspicuous left ventricular cardiac impulse, a third heart sound falling at its usual time, mitral or tricuspid regurgitation, bundle branch block, electrocardiographic changes denoting left ventricular hypertrophy or necrosis and more than slight cardiac enlargement radiologically.

In the absence of thromboembolic pulmonary hypertension, the left atrial pressure is usually 10 to 20 mm. Hg higher than the right in cases of cardiomyopathy, the divergence increasing with exercise; in chronic constrictive pericarditis, the two atrial pressures usually remain similar under all conditions. The implication that cardiomyopathic heart failure is initially and predominantly left-sided is accepted.

Wood, P.: "Chronic Constrictive Pericarditis," *Am. J. Cardiol.*, 7:48, 1961.

Editorial

Influenza Immunization

Autumn is the crucial time for protecting people in the high-risk groups against influenza. Because the occurrence and severity of influenza cannot be predicted accurately, the Surgeon General's Advisory Committee on Influenza recommends routine annual immunization for these groups — the aged, the chronically ill, and pregnant women. For maximum protection, these people should be fully immunized before winter sets in.

Influenza viruses of one type or another are almost constantly present in a few people everywhere. The general population develops some degree of immunity against them. A "crash program" of immunization is indicated when a variant strain of virus crops up or when an established strain goes on a rampage, but certain groups of people are always vulnerable to a special degree and protection must be extended to them on a continuing annual basis.

The definition of these high-risk groups is of significance to the chest physician. Many, perhaps most, of his patients fall into the high-risk category. Individuals in the following classifications require routine immunization:

1. Persons of all ages with chronic debilitating disease, particularly:
   - A. Patients with rheumatic heart disease, especially those with mitral stenosis.
   - B. Patients with other cardiovascular diseases, such as arteriosclerotic or hypertensive heart disease; especially those with evidence of frank or incipient cardiac insufficiency.
   - C. Patients with chronic broncho-pulmonary disease: e. g., chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, and pulmonary tuberculosis.
   - D. Persons with diabetes mellitus.
   - E. Patients with Addison's disease.
2. Pregnant women.
3. All persons 65 years of age and older.

The susceptibility of these people to influenza is not necessarily greater than that of the population at large, but influenza places a severe stress on these people and it is more likely to threaten their lives.

This showed up dramatically in connection with the three epidemic waves of Asian influenza that occurred in this country after the strain was introduced in 1957. The two initial waves in 1957 and 1958 and the third wave during the first three months of 1960 were accompanied by approximately 86,000 deaths in excess of the number normally expected for the periods involved. Analysis of the mortality data shows

that almost 85 per cent of these deaths were attributed to pneumonia-influenza (33 per cent) and cardiovascular-renal disease (51 per cent). With each successive wave, the proportion of victims over 65 increased. During the third wave, three-fourths of the total excess deaths occurred in this older group.

Aqueous, polyvalent, killed-virus vaccines are available commercially. Recent vaccine evaluations indicate that they are from 60 to 75 per cent effective against influenza caused by virus Types A, A_1, A_2, and B. Their use is contraindicated only in persons with a history of allergy to eggs or chicken, or who have had a previous allergic reaction to an egg-produced vaccine.

For initial immunization, the recommended adult dose of multivalent vaccine is 1.00 cc. (500 CCA units) given subcutaneously on two occasions, at intervals of at least two months. Members of the Advisory Committee have found that the booster response from the second dose is greater with this interval. Of course, if an epidemic threatens, it might become expedient to revert to the two-week interval between doses. Preferably, vaccination should be completed by November 1. Persons who have had the initial immunizing series should be given a 1.0 cc. booster dose of the vaccine subcutaneously by November 1 of each succeeding year.

Routine annual immunization of high-risk individuals could drastically lower the unnecessary deaths associated with influenza. The chest physician is in a particularly strategic position to protect the vulnerable.

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Washington, D. C.
Chairman, Council on Public Health
American College of Chest Physicians

*Assistant Surgeon General, Deputy Chief, Bureau of State Services, Public Health Service, U. S. Department of Health, Education, and Welfare.

POSTPERICARDIOTOMY SYNDROME

The postpericardiotomy syndrome occurred in 30 patients among 100 consecutive survivors of open heart surgery, utilizing the heart-lung machine, for repair of atrial and ventricular septal defects and the relief of pulmonic and aortic stenosis. Four patients experienced recurrences. Although an immediate traumatic pericarditis that can be demonstrated and followed by serial electrocardiograms develops in all patients undergoing wide incision and exploration of the pericardium, a delayed pericardial reaction, sometimes with pleural and pulmonary involvement, develops in approximately 30 per cent. This syndrome probably represents a hypersensitivity reaction to blood in a pericardial sac that has already undergone traumatic pericarditis.

Engle, M. A., and Ito, T.: "The Postopericardiotomy Syndrome," *Am. J. Cardiol.*, 7:73, 1961.

PRESIDENTIAL ADDRESS*

Hollis E. Johnson, M.D.
Nashville, Tennessee

Someone has suggested that there should be a renaissance of idealism among physicians. As I considered this suggestion, it came to my mind that there has never been an actual decline in the doctor's idealism, but rather a decline of the esteem and affection in which he has traditionally been held by this fellow man.

I believe there are four reasons for this change in attitude. First, there have always been those practitioners who have brought just criticism upon themselves and indirectly upon the whole medical profession by their inept acts. They have not served well the sick and those who thought they were sick. Second, the practice of medicine has been under scrutiny by government officials seeking to change our way of life. Third, the casual thrill of medicine has been played upon by writers. Sinclair Lewis in his novel, *Arrowsmith, M.D.*, held up unfortunate examples within the profession as characteristic of all its members. On occasion, recognized shortcomings of a few of our colleagues have been given publicity by others. The fourth reason stems from the fact that medicine in all its fields has become so complex. More time has been required for training both undergraduate and graduate. Less time has been left for the doctor to live in the manner of other men — less time for him to participate in religious, civic and political affairs. All these factors have had a withering effect upon the esteem in which the profession has been held for centuries.

It has been shown that almost everyone looks upon his personal physician as a paragon of virtue in whom one can confidently place his trust, and indeed his very life, without reservation; but without pause, this same person will express his doubts about the rest of the profession! It is my opinion that this attitude is the result of the adverse criticism and of the thoughtless acts of a few doctors and must not indicate a decline in the doctors' idealism.

I believe that never before have there been more, percentagewise, who are practicing medicine with the ideal conduct and service to mankind as there are today. This age in which we live has produced Albert Schweitzer who epitomizes the ideals of Hippocrates and the Great Physician in this respect: to serve man is to serve God. What doctor, and indeed what informed person, does not know and thrill to the accomplishments of Tom Dooley and his band of doctors who, to quote the introduction to his, *The Edge of Tomorrow*, built hospitals in the Laotian villages of VanVieng and Nom-Tha: ". . . within the shadow of Communist hatred learned how to convince people who had stoically borne pain and sickness as a part of life, that they could be helped . . . and learned how medical aid could reach the hearts and souls of a nation . . ." It is most gratifying and significant that some of the Fellows of this College have participated actively in this great work.

It will be said that these are unusual examples — but are they? There are many physicians who are rendering unselfish service to unfortunate people all over the world. Through these physicians, thousands of hours of service are given to needy people; however, these acts are so commonplace that they attract no notice. Harvey Cushing, in his Consecratio Medici, expresses it admirably in the words: "So let us believe, for our purposes at least, that 'devotion' not only implies a high standard of self-effacement, but still carries something of its quondam religious significance. And it is of the doctor's consecration to his task that I wish to speak, the kind of unselfish relation to suffering humanity that made St. Luke the beloved physician no more nor less than it makes many another doctor of name unheard and unsung today."

In my own state of Tennessee we have a law written and sponsored by the state medical association which creates a partnership between doctors and the state. By this law, the members of the state medical association agree to treat free of charge any person whom the state will declare indigent and will hospitalize at state expense. This makes available the best of medical and surgical care for any person regardless of his financial status. The doctors are doing no more than they have always done, but this law makes it official and assures all these people of hospitalization.

One does not have to remind the new Fellows that the lot of the medical student, both undergraduate and graduate, is a strenuous one — exacting and time-consuming with very little time left for recreation and the pursuit of pleasure. I wish it were

*Presented at the Convocation, 27th Annual Meeting, American College of Chest Physicians, New York City, June 25, 1961.

within my power to pay them fitting tribute, for such is long overdue! Perhaps some day a man of unusual eloquence will address an expressive note of recognition for their unusual, unselfish and almost unnoticed devotion to the task of relieving human suffering. No doubt they would deny any altruistic motives, yet in the words of Dr. William Allen Pusey: "The emotion, particularly the altruistic rewards of the practice of medicine are among its chief satisfactions. The sum total of the doctor's effort for his patients is constructive. He can relieve suffering; he can overcome defects; he can bring men and women back to happiness and usefulness; he can aid in the physical betterment of childhood; sometimes he can save a life. Sometimes he cannot do any of these things, but on the whole, the balance is in his favor. Of course, sensible men in the practice of medicine waste no time in self-congratulation, but the knowledge of these advantages exists in the subconsciousness of every intelligent physician and gives to medicine an attractiveness that is unsurpassed and that is equaled by few careers."

Dr. Herman Moersch had this to say in an editorial in the College journal, *Diseases of the Chest:* "History eloquently records that two of the dominant forces in the betterment of man have been religion and the healing art. Most important of all for the physician, his prerequisite of medicine, must of necessity imply a love of humanity."

Dr. Henry Boorsook, in the 1957 Franz Groedel Memorial Lecture, reminds us that medicine must always be an art as well as a science and that sympathy is necessary for its fullest application.

Many other quotations can be cited to emphasize that the practice of medicine implies idealism, but these are sufficient to emphasize our point. A sign of our times is a denial from men of medicine that they have any altruistic motive in their work. It is not fashionable to acknowledge such sentiment. Should one be so seized with curiosity as to look persistently for the truth of this matter, he will find that most physicians are actuated in their relationship to their profession by a deep desire to be of service to people. The deep hidden fear of ridicule or of being labeled a non-conformist keeps them from realizing or acknowledging their true feelings and their motives. It must be recognized that the good may be hidden as well as the bad.

Knowing that altruism and idealism are part of the force that drives doctors, we can start regaining our position in the hearts of our people by admitting our feelings, if only to ourselves. We must give of ourselves freely to all who seek our help, not only in the science of medicine, but in the art as well. We must consider the whole man.

The basic idea of the practice of medicine is individual service to the individual person. Failure to emphasize this and to adhere to this principle can lead only to a loss of confidence in doctors. We must maintain the idea that the patient comes first. The sick person is usually not interested in anything but his personal problems and he wants his doctor to realize that and to treat him accordingly!

The doctor's second obligation is to his community and its health and the safeguarding of that health because that is his profession. He has other obligations to his neighbors. Doctors must become active in all phases of community affairs. No one doctor can participate in all these affairs, but as a profession we must be represented in all such worthwhile activities.

Doctors cannot afford to shun politics and leave all governmental activities to other people. Because of their broad education, physicians are well fitted to play leading roles in all phases of political life; if they do not, they will become the victims of pressure groups who exert their unrestrained influence upon the politicians. They must carry the message to the public that the physician who is active politically is moved by the same ideals in politics that motivate him as a practitioner of medicine! That he is indeed someone's personal physician and is interested in the community problems of health and welfare and in the maintenance of personal freedom.

If we do all these things and are able to convince the public of our sincerity of purpose in their behalf, we shall have restored our profession to its former position of high esteem in the hearts of all. We shall have justified the paraphrasing of Josh Billings' statement concerning the strawberry: "God may have made a better man than a good doctor, but doubtless he never did."

COLLEGE INTERIM SESSION

The Interim Session of the College will be held in Denver on Saturday and Sunday, November 25 and 26, 1961, at the Brown Palace Hotel. The American Medical Association will hold its Clinical Meeting in Denver, November 27 through 30.

A scientific program will be presented on Saturday morning and Sunday afternoon, with round table luncheons and fireside conferences on Sunday. A dinner sponsored by the Colorado Chapter of the College will be held on Saturday night. The complete program appears in the September issue of *Diseases of the Chest*. Additional copies may be obtained by writing the Chicago offices of the College at 112 East Chestnut Street.

The Board of Regents and Board of Governors of the College will hold a joint luncheon on Saturday, to be followed by the semi-annual meeting of the Board of Regents.

CHAPTER NEWS

Southern Chapter

The 18th annual meeting of the Southern Chapter will be held at the Sheraton Dallas Hotel, Dallas, November 4 and 5. Scientific sessions will be held in the Austin room and the luncheon will be in the Travis room. The program follows:

Saturday afternoon, November 4 — *Chairman:* DeWitt C. Daughtry, Miami, President, Southern Chapter

1:00 p. m. Symposium on Cystic Pulmonary Disease

Pulmonary Cystic Problems in Pediatric Practice
Robert R. Shaw, Dallas

Further Observations on Congenital Lobar Emphysema
Sam E. Stephenson, Jr., Nashville

Cystic Pulmonary Disease in the Adult
Daniel E. Jenkins, Houston

Bullous Emphysema: Clinical Course and Counter-Measures
Charles E. Andrews, Morgantown, West Virginia

Patient Selection: The Secret of Success in Emphysema Surgery
Osler A. Abbott, Atlanta

3:15 p. m. Panel discussion — Pulmonary Cystic Disease
Moderator: John H. Seabury, New Orleans

Panel:

Internists:	Charles E. Andrews, Morgantown
	Daniel E. Jenkins, Houston
	John A. Wiggins, Jr., Fort Worth
Pathologist:	Robert M. O'Neal, Houston
Radiologist:	Marvin R. Gunn, Beaumont
Surgeons:	Osler A. Abbott, Atlanta
	Edward R. Munnell, Oklahoma City
	Robert R. Shaw, Dallas

Sunday morning, November 5 — *Chairman:* Donald L. Paulson, Dallas, Secretary, Texas Chapter

9:00 a. m. Patent Ductus Arteriosus in Early Infancy
Masauki Hara, William T. Dunga, Ben M. Lincoln and Frank McCutcheon, Little Rock

Medical Aspects of Heart Block
Charles R. Cain, Dallas

Surgical Management of Heart Block
Harold C. Spear, DeWitt C. Daughtry and John G. Chesney, Miami

Technical Considerations in Open Surgery on the Aortic Valve
Milton V. Davis, Ben F. Mitchell and Maurice Adam, Dallas

Practical Significance of Coronary Artery Anomalies with Report of First Successful Surgical Correction of an Anomalous Left Coronary Artery in an Adult
Hu A. Blake, Fort Sam Houston, Texas and William C. Manion, Washington, D. C.

11:00 a. m. Eighth Annual Paul A. Turner Memorial Lecture — Mycobacterial Infection in Man
John S. Chapman, Dallas

12:00 noon Luncheon
International Medicine
Robert R. Shaw, Dallas

Sunday afternoon — *Chairman:* Carlos J. Quintanilla, Harlingen, Texas, President, Texas Chapter

1:30 p. m. Bronchopulmonary Diseases

Puzzling Chest X-ray Findings Associated with Primary Abdominal Disease
John N. Bickers and Howard A. Buechner, New Orleans

Role of Heated Aerosols as a Diagnostic and Therapeutic Tool in Management of Bronchopulmonary Disorders
William F. Miller, Ivan E. Cushing and Don Warden, Dallas

An Intrinsic Origin of Bronchospasm
John E. Rayl, Kjell H. Christiansen and John T. Joyner, Oteen, North Carolina

The Myth of IPPB/I
Watts R. Webb, G. D. Campbell and V. deGuzman, Jackson, Mississippi

Management of Bronchopulmonary Infections in Patients with Impaired Resistance due to Various Causes
J. Lewis Yates, H. V. Langeluttig and Charles A. Brasher, Mt. Vernon, Missouri

3:30 p. m. *Chairman:* Henry R. Hoskins, San Antonio, Vice-President, Southern Chapter

Non-opaque Foreign Body Bronchiectasis
H. Bieman Othersen and Wendell B. Thrower, Charleston, South Carolina

Hemoptysis: Diagnosis Essential to Proper Management
Robert E. Carr, Fort Worth

Comparative Study of 100 Consecutive Cases of Hemoptysis
Maurice Adam, Milton V. Davis and Ben F. Mitchell, Dallas

Experiences with Bronchial Carcinoma Among a Rural Population
Hugh E. Stephenson, Robert E. Paulette, Thomas G. Sutterfield and William Dowdy, Columbia, Missouri

A Favorable Form of Bronchial Carcinoma: A Reminder that Such Exists
Joseph W. Peabody, Jr., Sol Katz, William S. Lyons and Edgar W. Davis, Washington, D. C.

Austrian Chapter Organized

The Austrian Chapter of the College, the 84th to be established, was organized on May 13 by Prof. Anton Sattler, Vienna, Regent of the College for Austria. The following officers were elected:

President	Felix Mlczoch, Vienna
Vice President	Ernst Ruckensteiner, Innsbruck
Secretary-Treasurer	Herbert Sighart, Vienna

NEW CHAPTER OFFICERS

Arizona Chapter

President	Andre J. Bruwer, Tucson
Vice President	Fred W. Coleman, Jr., Phoenix
Secretary-Treasurer	Bertram L. Snyder, Phoenix (re-elected)

Florida Chapter

President	Charles F. Tate, Jr., Miami
Vice President	Harold W. Johnston, Orlando
Secretary-Treasurer	Dwight J. Wharton, Jacksonville

Kansas Chapter

President	Benjamin M. Matassarin, Wichita
Vice President	John G. Shellito, Wichita
Secretary-Treasurer	John L. Morgan, Emporia

Minnesota Chapter

President	W. Robert Schmidt, Minneapolis
Vice President	Coleman J. Connolly, St. Paul
Secretary-Treasurer	James Bellomo, St. Paul

New York State Chapter

President	Alfred S. Dooneief, Mt. Kisco
1st Vice President	Hyman Alexander, New York City
2nd Vice President	J. George Lang, New York City
Secretary-Treasurer	Harry Golembe, Liberty (re-elected)

Ohio Chapter

President	Joseph T. Tomashefski, Columbus
Vice President	Harold G. Curtis, Cleveland
Secretary-Treasurer	Francis G. Kravec, Youngstown (re-elected)

Philippine Chapter

President	Enrique M. Garcia, Quezon City
President-Elect	Fidel Nepomuceno, Manila
Vice President	Benito C. Garcia, Rizal
Secretary-Treasurer	Priscilla J. Tablan (re-elected)

SCIENTIFIC NEWS ITEMS FROM THE 27th ANNUAL MEETING

AMERICAN COLLEGE OF CHEST PHYSICIANS

Circulation in Newborn Lambs with Respiratory Distress

Klara J. Prec and LeClaire Leslie, Chicago, stated that Caesarean section frequently leads to the development of respiratory distress in newborn lambs for reasons as yet undetermined. Symptoms in these animals are similar to those observed in newborn infants with the respiratory distress syndrome. Histologic sections of the lung and ductus arteriosus were studied in lambs sacrificed or which succumbed to their difficulties. Nine lambs with respiratory distress were scrutinized and results were compared with those obtained from 38 healthy lambs studied in their laboratory. Ten were delivered by Caesarean section, while 28 were born spontaneously. Respiratory distress did not occur in lambs delivered via the birth canal; therefore, Caesarean section appears to be implicated in some way in the causation of this disorder. Histologic sections showed varying degrees of atelectasis without definite hyaline membrane formation. The most striking laboratory finding was a high proportion of left to right shunt curves in animals with respiratory distress, while this type of curve was only rarely seen in healthy newborn lambs. However, these shunts were rarely very large as judged by the disappearance time/build-up time ratio.

Delivery Process and Cardiovascular System in Newborn

L. Stanley James, New York City, studied the neonatal circulation by means of intracardiac pressures, phonocatheters, blood sampling, intracardiac hydrogen electrode, and cineangiography. At delivery, the infant is by adult standards grossly hypoxic. The range of oxygen values observed, the relationship of these values to pH and carbon dioxide tension, and the pattern of recovery over the first hours all suggest that there has been some interference with exchange of oxygen and carbon dioxide between mother and fetus during the final stages of delivery. Infants who are more asphyxiated at birth are more acidotic and show a slower rate of recovery than is observed in vigorous infants. The transverse diameter of the heart is greater in the asphyxiated group and becomes smaller over the first five days of life. The enlarged cardiac silhouette has been shown to be associated with regurgitation through the mitral valve in some instances and an abnormal left to right shunt through the foramen ovale in others. These abnormal hemodynamics appear to be the result of asphyxia on the myocardium.

Cardiac Surgery in Infancy

Peter V. Moulder, Chicago, pointed out that the number of cardiac procedures necessary in the infant group is increasing. This is due to the more proficient diagnostic ability of the pediatric cardiologists, awareness of cardiologic emergencies in children by all pediatricians, and ability to perform surgical procedures at this time which can be reparative and palliative. Most surgical procedures in infancy are done after sufficient trial of medical management. It is obvious that the great majority of congenital defects of an operable nature actually do carry on through this period of time and that also there is a large number of patients with untreatable defects who die, especially in the first few days of life. He also emphasized that reparative operations can be applied to patent ductus arteriosus, coarctation of the aorta, pulmonary valve stenosis and possibly to ventricular septal defects. Palliative operations can be applied to pulmonary valvular stenosis, ventricular septal defects (pulmonary artery banding), and in a variety of cyanotic heart malformations with shunts from a systemic to pulmonary artery or superior vena cava to pulmonary artery.

Viral Myocarditis in Infancy and Childhood

Henry R. Shinefield, New York City, called attention to the fact that recent advances in tissue culture techniques have resulted in isolation of viruses responsible for myocarditis in infants and children. The group of viruses most commonly implicated as the etiologic agent is the Coxsackie Group B, types 2-5, which have been isolated from the stool and blood of cases that have been clinically suspect. Postmortem study of fatal cases has resulted in recovery of Coxsackie viruses from the myocardium, the brain and other viscera. Other viral illnesses such as poliomyelitis and influenza may be complicated, on occasion, by myocarditis. He said that prominent clinical symptoms and signs in infants include dyspnea, tachypnea, tachycardia, cyanosis, listlessness, poor feeding and rapidly enlarging livers. The course of illness in these infants is usually rapid and fatal; however, some infants have survived. In older children, the disease may be milder than that observed in infants and is usually not accompanied by generalized systemic involvement.

Pathology of Myocarditis

William C. Manion, Washington, D. C., presented illustrative instances of true myocarditis gathered from the files of the Armed Forces Institute of Pathology and from other sources. He emphasized that true myocarditis is not a rare disease, but rather a frequent occurrence during the course of many bacterial, rickettsial, viral, fungal and parasitic diseases. It is an occasional result of physical and metabolic changes, as well as toxins. He said that a more careful study with multiple sections from the heart may reveal a higher frequency of myocarditis in many of the diseases and serve to bring about a closer correlation between the clinical signs and histologic evidence of heart involvement.

Bronchography and Bronchoscopy in Emphysema and Chronic Bronchitis

The advantages of bronchoscopy and bronchography in obtaining a correct diagnosis, as well as the finer details of the mucosal pattern were elaborated by John H. Hirschfeld and co-workers of Baltimore. In emphysema as well as in chronic bronchitis, inspection of the mucosa by means of the endoscopic telescope reveal pitted, sunken-in areas or sinus-tracts simulating holes which represent the dilated openings of cystically enlarged hypertrophied bronchial mucous glands. Subsequent bronchography confirms endoscopic findings in nine of ten cases. They showed typical bronchographic findings of "chronic deforming bronchitis" such as constriction upon the point of ramification, dilated and cystic bronchial mucous glands, secretory plugs, secretory stops, "string of beads" formation and transition to bronchiolectasis and bronchiectasis. It was also shown that these findings frequently accompany emphysema. Other bronchographic findings in emphysema, such as the "tree stump" effect, the "dead or leafless tree" effect were demonstrated.

Effectiveness of IPPB Therapy

Theodore H. Noehren and Paul T. Schnatz, Buffalo, related that the maximum effective ventilation from mechanical assistance, such as intermittent positive pressure breathing, is dependent upon several important variables, including pressure, rate of air flow, lung volume, respiratory rate, bronchial obstruction, and the shape of the pressure curve. The influence of these variables was illustrated by the use of ether clearance as the method of definition. The results revealed why IPPB may not be as effective in some situations as in others. It was also demonstrated that the effectiveness of this type apparatus can be improved in the management of pulmonary emphysema.

Role of Host Resistance in Natural History of Cancer

Physicians have observed in the natural history of cancer spontaneous remission, post-surgical regression of remaining lesions, regression of lesions distant from irradiated tumor masses, and sudden renewed growth of metastatic nodules many years following removal of parent tumors. These observations implicate host resistance as a factor in the course of the disease. Volunteer patients having terminal cancer were studied by Russell H. Wilson *et al.* of Dallas. The work on the first five patients was a pilot study with deep x-ray therapy. The remaining 18 received intramuscular injections of their tumor antigen in Freund's adjuvant. Blood was withdrawn weekly before and after radiotherapy or the intramuscular injections of the antigen. The serum antibody titers were measured with the tannic acid treated sheep erythrocyte agglutination test. Three of the five patients having deep x-ray therapy showed a significant antibody titer rise suggesting need for further studies with a more direct approach. It was noted that metastatic nodules distant from the irradiated mass regressed with the rise in antibody titer.

An inflammatory reaction characterized by erythema, swelling, edema, heat and tenderness at the tumor site was noted 15 to 25 days following injection of the antigen. *In vivo* cytotoxicity studies were conducted with the Cohn fraction I, II and III. Sixty-three per cent of the injected subcutaneous nodules became nonpalpable within a period of ten days. Five per cent grew and became measurable again before the patient expired. Reintroduction of the antibody protein caused the nodules to become nonpalpable. These same Cohn fractions had no effect on the patient's normal tissue. These data indicate that an humoral cytotoxic antibody can be elicited by an injection of autologous tumor homogenized in Freund's adjuvant.

Treatment of Post-Resectional Bronchial Fistula

Victor Manuel Betancourt and Javier Garcia Zepeda, Mexico City, Mexico, developed a new approach for the closure of post-resectional bronchial fistulas by producing submucosal fibrosis. Experimental work in dogs, with subcutaneous injection of a chemical irritant, preceded clinical application of this method. The solution employed is NaOH with lyophilized placenta. Satisfactory results were obtained in 47 of 50 cases, with three failures (two of the failures had incomplete treatment).

Coronary Blood Flow Measured by Electromagnetic Flowmeter

A compact, noncannulating electromagnetic flow meter of the Kolin type was developed by Major Robert J. Hall, Edward M. Khouri and Donald Gregg, Washington, D. C. It has a linear response in the range utilized. Circumflex coronary artery blood flow was measured in 14 dogs. Measurements were performed with the chest open in ten dogs and chronic repetitive flow curves were recorded in the unanesthetized, closed dog over a one to four-week period post-implantation in four animals. Observations were made upon the effect of reactive hyperemia and intracoronary drug administration. Phasic flow curves were of the contour noted by older techniques. Smaller, more compact probes now permit the recording of total left coronary artery flow in the intact animal.

Newer Applications of Pulmonary Angiography

Osler A. Abbott and Britt B. Gay, Atlanta, stated that with the advent of rapid cassette changers and cineangiography, increased information can be obtained (because of the multiple film studies available) relative to each of three basic phases of the pulmonary circulation, namely: a) arterial phase; b) capillary phase; c) venous phase. They said there is a practical value of pulmonary angiography in the study and management of patients with pulmonary emphysema, often revealing a localized increased severity of disease resulting in a definitive surgical attack upon this disease entity. In bronchiectasis, the findings closely parallel the bronchographic study and aid in the selection of patients for segmental resection. Their parallel studies of pulmonary function and pulmonary angiography suggest that pulmonary angiography may become a valuable adjunct objective study of pulmonary function. In their opinion, this procedure may have some value in the evaluation of peripheral pulmonary masses, particularly in regard to pulmonary infarction. Also, they found that pulmonary venous pattern in detail has revealed certain specific abnormalities in association with pulmonary neoplasm.

Reduced Cardiac Sympathetic Tone and Myocardial Function

The ventricular responses to the increased filling pressure (right atrial mean pressure) produced by tilting into the headdown position were studied by John W. Eckstein and A. W. Horsley, Iowa City, using ten vagotomized dogs treated with gallamine. Cardiac output was obtained from continuously recorded concentration curves of indocyanine green dye. Pressures were recorded from the systemic and pulmonary arteries, right atrium and pulmonary wedge position. Before administration of a ganglionic blocking agent, there were no significant changes in heart rate, minute volume, stroke volume or external work of either ventricle in response to increased atrial pressure. After cardiac sympathetic tone was reduced by administration of ganglionic blocking agent (trimethidinium) heart rate, minute volume, stroke volume and ventricular work fell. Restoration of atrial pressure caused significant increases in these functions. Restoration of the ventricular rate by pacing the atrium electrically caused no further increase in minute volume or work, but stroke volume and work fell appreciably.

It is suggested that the increased atrial pressure before trimethidinium causes no change in cardiac output or work because of reflex withdrawal of sympathetic tone to the myocardium and consequent shifting of the ventricular function curve to the right. The pharmacologically denervated heart with its rate controlled seems to operate on a lower ventricular function curve and appears to increase its output only with an increase in filling pressure. Its behavior resembles that of a heart-lung preparation.

Open Heart Surgery in a Community Hospital

One hundred consecutive cases of congenital or acquired cardiovascular disease undergoing surgery were reviewed by Clair E. Basinger and Richard A. Rasmussen, Grand Rapids, Michigan. Although open heart surgery was initiated in university medical centers, the authors have had the unique experience of developing and maintaining open heart surgery in a private community hospital. For the past five years, a team necessary for this project has been in operation. A complete cardiac diagnostic unit, experimental research laboratory and a cardiopulmonary laboratory were established. The necessary technical assistants were obtained and trained. Basic techniques were perfected in the laboratory and then applied in the operating room. Pediatric and adult intensive care units for the postoperative open cardiotomy patient, as well as other acutely ill patients, have been a direct result of this project.

ANNOUNCEMENT

Dr. J. R. Bignall, Dean of the Institute of Diseases of the Chest, London, England, has announced that the Institute will present the following postgraduate courses:

Autumn term (October to December, 1961)

1. Full-time course in tuberculosis
2. Part-time course in diseases of the chest
3. Full-time course in thoracic surgery
4. Part-time course in chest radiology

Spring term (January to March, 1962)

1. Full-time course in disease of the chest, as well as courses 2, 3, and 4 listed above.

Summer term (April to July, 1962)

1. Full-time combined course on diseases of the heart and lungs (in conjunction with the Institute of Cardiology) and courses 2, 3, and 4 as above.

Interested physicians may write to the British Postgraduate Medical Federation, 18 Guilford Street, London W.C.1, or to Dr. Bignall, for full information.